

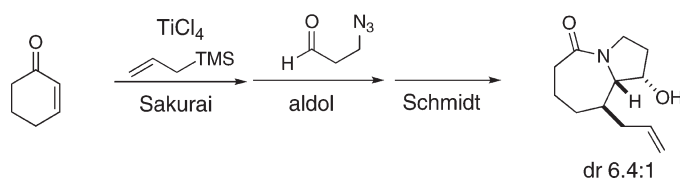
One-Pot Synthesis of Lactams Using Domino Reactions: Combination of Schmidt Reaction with Sakurai and Aldol Reactions

Chan Woo Huh, Gagandeep K. Somal, Christopher E. Katz, Huaxing Pei, Yibin Zeng, Justin T. Douglas, and Jeffrey Aubé*

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott Hall, Room 4070, University of Kansas, Lawrence, Kansas 66045-7582

jaube@ku.edu

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A series of domino reactions in which the intramolecular Schmidt reaction is combined with either a Sakurai reaction, an aldol reaction, or both is reported. The Sakurai reaction of an allylsilane with an azido-containing enone under Lewis acidic conditions followed by protonation of the resulting titanium enolate species allowed for a subsequent intramolecular Schmidt reaction. Alternatively, the intermediate titanium enolate could undergo an aldol reaction followed by the intramolecular Schmidt reaction to form lactam products with multiple stereogenic centers. The stereochemical features of the titanium enolate aldol reaction with several 3-azidoaldehyde substrates during this domino process is discussed.

Introduction

Domino reactions, in which two or more reactions are carried out sequentially in one pot, have the potential of increasing efficiency over traditional multistep processes.¹ Our continuing efforts to explore the Lewis acid promoted reaction of alkyl azides^{2,3} led us to consider combining that reaction into a domino sequence with C–C bond-forming reactions that use similar conditions. Along these lines, we have previously reported the domino Diels–Alder/intramolecular Schmidt reaction and described its use in natural product and library synthesis (Scheme 1).^{4,5} The first step of

this sequence is a Lewis acid-promoted Diels–Alder reaction between azido-containing diene **1** and enone **2**. In the second stage, the in situ generated ketone **3** undergoes intramolecular azide addition to form azidohydrin **4** and subsequent Schmidt rearrangement^{2,3} to generate bicyclic lactam **5** in 82% yield. Under these conditions, Schmidt rearrangement does not occur prior to the Diels–Alder reaction because of the low reactivity of azides toward ketones in an intermolecular setting. Other laboratories have also begun to examine the utilization of the Schmidt reaction in a domino reaction context.⁶

A logical next step was to study the combination of other Lewis acid promoted reactions with the intramolecular Schmidt reaction. For example, the Sakurai^{7,8} and aldol reactions are typically mediated by Lewis acids similar to those used in the intramolecular Schmidt rearrangement. Furthermore, both the Sakurai reaction/protonation of

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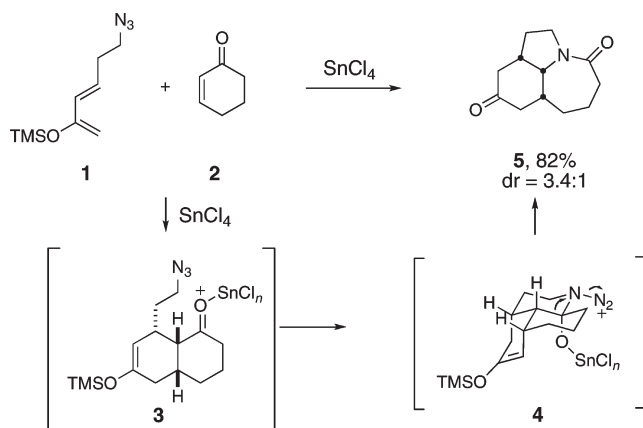
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SCHEME 1



enones and the aldol reaction furnish ketones suitable for a downstream Schmidt reaction. Herein, we describe the development of new Sakurai/Schmidt, aldol/Schmidt, and Sakurai/aldol/Schmidt sequences.

Result and Discussion

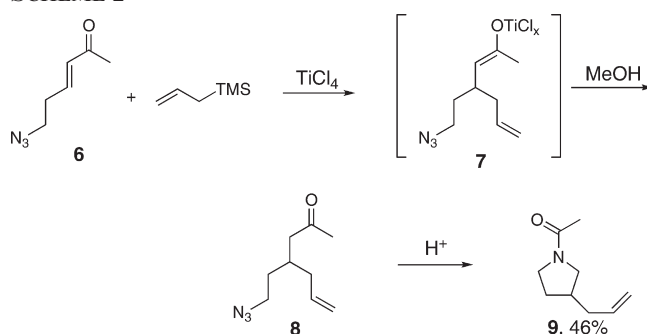
Domino Sakurai/Schmidt Reaction. We envisioned an enone containing an appropriately tethered alkyl azide would react with allyltrimethylsilane under Lewis acidic conditions to form a ketone following protonation, thus allowing for a subsequent intramolecular Schmidt reaction (Scheme 2). We had previously demonstrated that *trans*-enones, like that present in **6**, do not allow for an intramolecular Schmidt reaction in **6** prior to double-bond modification.⁵ Reaction of **6** with allyltrimethylsilane in the presence of TiCl_4 followed by protonation of the resulting titanium enolate **7** and subsequent intramolecular Schmidt reaction led to a lactam **9**. The best conditions involved initial treatment of **6** with 2 equiv of TiCl_4 and allyltrimethylsilane at -78°C for 2 h. The reaction temperature was brought to 0°C over 4–5 h followed by the addition of 5 equiv of methanol. Methanol acts as the proton source for the titanium enolate **7** to generate ketone **8** in situ. After methanol was added, the reaction was stirred at room temperature for an additional 45 min for the completion of the Schmidt reaction before quenching with a saturated solution of ammonium chloride. It seems that hydrochloric acid, generated from the reaction between methanol and TiCl_4 , is acidic enough to mediate the subsequent intramolecular Schmidt reaction to give lactam **9** in 46% yield.⁹

We also prepared and tested azide-containing cyclic enone substrates **10**³ and **11** under similar conditions (Scheme 3). When azide **10** was submitted to Sakurai/Schmidt conditions, lactam **14** was obtained in 75% yield (*cis/trans* 7:3) with methanol and 79% yield (*cis/trans* > 9:1) with *tert*-butyl alcohol, respectively. The improved selectivity with bulky *tert*-butyl alcohol over methanol could be indicative of an increased steric interaction with the pseudoequatorial allyl group as shown in **13**, which allows for a more favorable

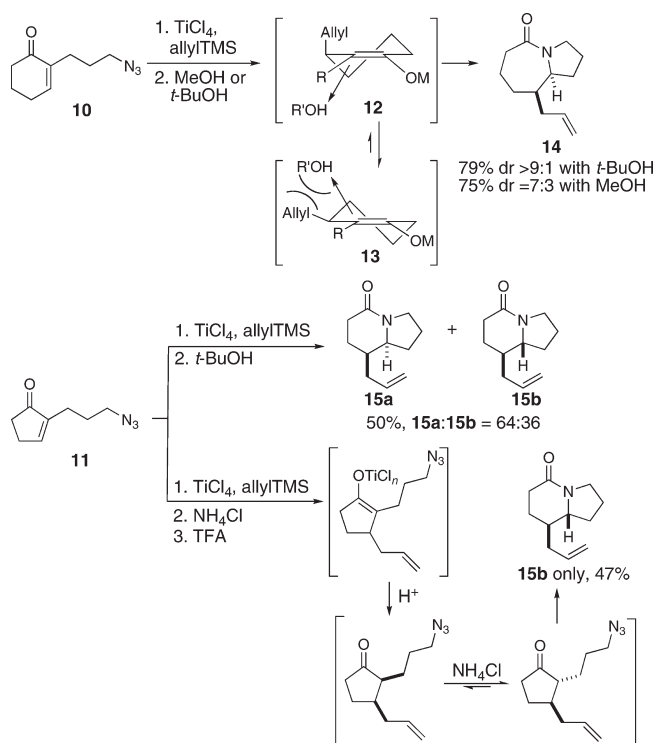
(9) Control experiments established that related intramolecular Schmidt reactions are not promoted by $\text{Ti}(\text{O}i\text{-Pr})_4$.

(10) An analogous steric interaction between an incoming allylsilane nucleophile and an alkyl group in the 3-position of the half-chair oxocarbenium ion was discussed by Woerpel. See: Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169.

SCHEME 2



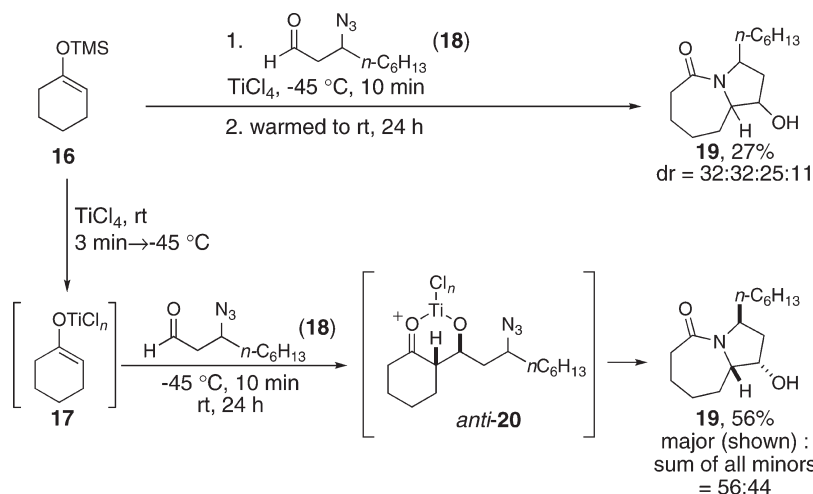
SCHEME 3



attack from the alternate conformation **12**.¹⁰ Azide **11** similarly led to lactam **15** in 50–66% yield but with much lower stereoselectivity (**15a/15b** = 64:36). In this case, the outcome was not affected by the nature of the proton source. An analogous two-stage procedure in which the Sakurai-induced enolate was quenched and equilibrated with aqueous saturated NH_4Cl solution followed by treatment with TFA resulted in the exclusive formation of thermodynamic **15b** in overall 47% yield for the sequence. Compounds **15a** and **15b** were assigned as drawn from mechanistic considerations. Kinetic protonation of the enolate resulting from the allylation reaction should afford the 2,3-*cis* ketone intermediate affording lactam **15a** following Schmidt reaction. This was confirmed by the exclusive formation of **15b** when an equilibration step was inserted into the sequence, as this lactam should be derived from the thermodynamically more stable *trans* cyclopentanone intermediate shown.

Domino Aldol/Schmidt reaction. We envisioned that the aldol reaction between an enolate equivalent and an azide-containing aldehyde would provide a Schmidt substrate

SCHEME 4



suitable for the development of another domino reaction. To this end, we examined various versions of aldol reactions for silyl enol ether **16**. Thus, treatment of the silyl enol ether **16** with TiCl_4 in the presence of an aldehyde should enact a Mukaiyama aldol reaction.¹¹ In contrast, aging a solution of **16** and TiCl_4 leads to titanium enolate **17** via transmetalation.¹² While silyl enol ether **16** is expected to react via an open transition state, **17** should go via a closed transition state.¹³ This difference could potentially give different outcomes with regards to stereoselectivity (Scheme 4).

Unfortunately, these domino reactions turned out to be synthetically impractical. The Mukaiyama aldol/Schmidt reaction produced lactam **19** as a mixture of all four possible diastereomers in 27% unoptimized yield. The outcome of the titanium aldol/Schmidt reaction was slightly better with a 56% yield and diastereomeric ratio of 56:44 (major/sum of three minor diastereomers). The structure of the major diastereomer was confirmed by X-ray crystallography and was shown to be derived from the *anti*-aldol product **20**. Although these domino aldol/Schmidt reactions were poorly stereoselective, they provided insight into the next domino reaction examined: the Sakurai/Aldol/Schmidt reaction.

Domino Sakurai/aldol/Schmidt Reaction. The above experiments involving domino Schmidt reactions utilizing aldol or Sakurai reactions led to the idea of combining all three reaction types. Although domino Sakurai/aldol reactions are known,^{7,14} no reaction combining a Sakurai reaction, an aldol reaction, and a Schmidt reaction has been reported.

Several 3-azidoaldehydes such as **18**,¹⁵ **21**,¹⁶ and **22**¹⁷ were tested for the domino Sakurai/aldol/Schmidt reaction (Scheme 5). The Sakurai reaction of allyltrimethylsilane and 2-cyclohexen-1-one (**2**) mediated by 1 equiv of TiCl_4 in

CH_2Cl_2 at $-45\text{ }^\circ\text{C}$ was completed in less than 1 h as confirmed by TLC monitoring. 3-Azidoaldehyde was then added, and the solution was warmed to $0\text{ }^\circ\text{C}$ to allow the aldol and Schmidt reactions to occur. Following workup, the desired lactam product was obtained in 36–42% yield with moderate to high diastereoselectivity (conditions A, Scheme 5). Under these conditions, aldol reaction did not occur unless the reaction mixture was warmed to $0\text{ }^\circ\text{C}$. At this temperature, both aldol and Schmidt reactions occurred, preventing us from isolating simple aldol products. Several other Lewis acids were also briefly surveyed (e.g., SnCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, MeAlCl_2) but led in all cases to inferior results.

The major product of the reaction between enone **2** and 3-azidoaldehyde **21** was **23a**, arising from an *anti*-aldol intermediate, in a 6.4:1 ratio. The only isolable minor product, **23b**, was the Schmidt product of the corresponding *syn*-aldol intermediate. An analogous reaction of 3-azido-nonanal (**18**) led to **25a** in 4:1 diastereoselectivity. Again, **25a** arose from an *anti*-aldol intermediate, whereas minor **25b** was from a *syn*-aldol intermediate. Surprisingly, even with additional stereogenic center, only two diastereomers were obtained (no additional isomers were observed in the ^1H NMR of the crude reaction mixture). Finally, bulky aldehyde **22** furnished **26a** as single diastereomer in 42% yield. In all cases, strict *trans* selectivity was observed for the addition across the cyclohexene double bond.

In considering ways of improving the yield of the reaction sequence, we hypothesized that both the aldol and Schmidt reaction steps were slow at $0\text{ }^\circ\text{C}$ and could be complicated by decomposition pathways at that temperature. Therefore, the procedure was modified by adding an additional 2 equiv of TiCl_4 at $0\text{ }^\circ\text{C}$ to facilitate the rapid completion of the Schmidt reaction (conditions B, Scheme 5). Upon addition of TiCl_4 , a moderate amount of bubbling was observed, which suggested that the additional acid did in fact accelerate the Schmidt reaction. The resulting mixture was kept at $0\text{ }^\circ\text{C}$ overnight (conditions B in Scheme 5). Using these conditions, we could obtain products in higher yields (56–59%), but the diastereoselectivity was decreased. The reaction of aldehyde **21** still furnished two diastereomers albeit with lower selectivity (2.6:1). With **18**, we began to observe two more minor diastereomers, which resulted in 1.8:1 selectivity for the major relative to the sum of all minor diastereomers.

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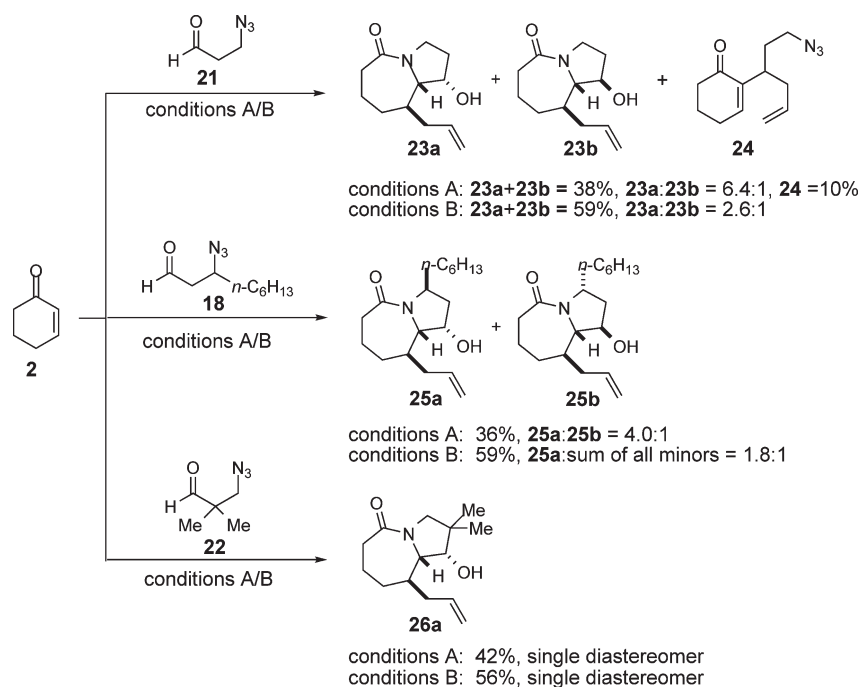
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SCHEME 5



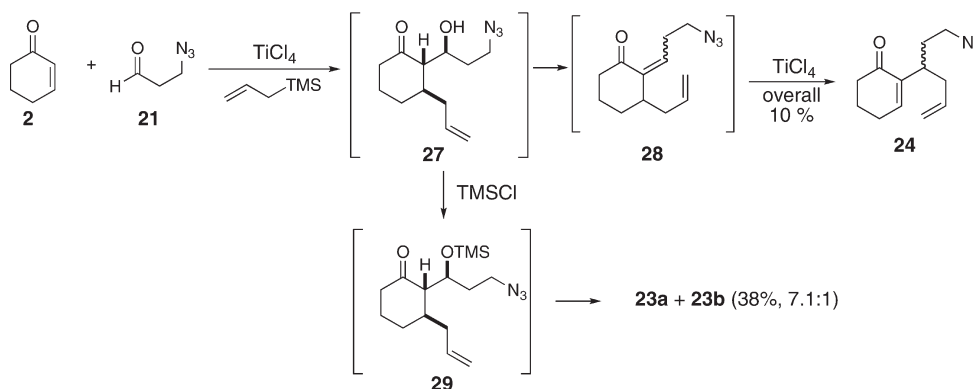
conditions A:

1. TiCl_4 (1 equiv.), allylTMS (1.4 equiv.) CH_2Cl_2 , -45°C , 1 h
2. 3-azidoaldehyde (1.6 equiv.), CH_2Cl_2 , -45°C , 10 min, then 0°C , 24 h

conditions B:

1. TiCl_4 (1 equiv.), allylTMS (1.4 equiv.) CH_2Cl_2 , -45°C , 1 h
2. 3-azidoaldehyde (1.6 equiv.), CH_2Cl_2 , -45°C , 10 min, then 0°C , 6 h
3. TiCl_4 (2 equiv.), 0°C , overnight

SCHEME 6



Sterically encumbered aldehyde **22** still provided a single diastereomer **26a** as the product even with harsher conditions.

The reaction between **2** and **21** was accompanied by formation of 10% of enone species **24** as a side product. This unexpected side product **24** could arise from β -elimination of aldol intermediate **27** followed by a precedented Lewis acid-promoted Cope rearrangement (Scheme 6).¹⁸ Enone **24** could in principle lead to additional side products via nucleophilic addition, although we did not identify any such byproducts. We anticipated that addition of excess amount of TMSCl (5 equiv) might slow down the rate of β -elimination of the aldol intermediate by trapping the initially

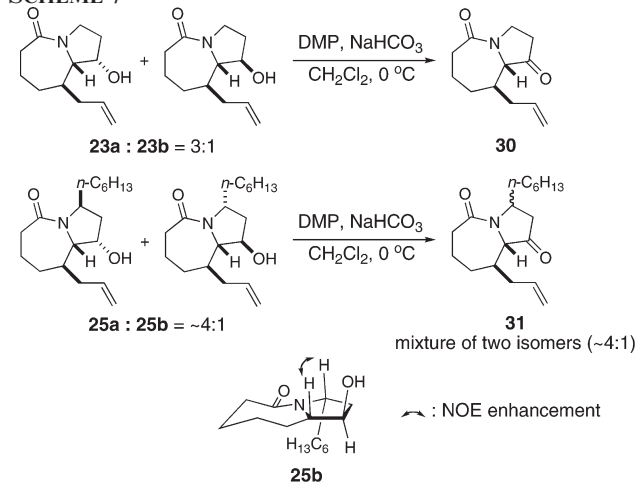
formed aldol adduct **27** as its TMS ether derivatives **29**, thus give more chance for the Schmidt reaction to occur. Although the stereoselectivity was slightly improved (7.1:1) by adding TMSCl, the overall yield remained the same (38%).

The structures of the three major diastereomers **23a**, **25a**, and **26a** were confirmed by X-ray crystallography. The configuration of minor diastereomer **23b** was determined by oxidizing the mixture of **23a** and **23b** by Dess–Martin periodinane,¹⁹ which resulted in formation of a single ketone **30**. However, the oxidation of the mixture of **25a** and **25b** afforded **31** as a mixture of two products. The structure of minor diastereomer **25b** was further confirmed by NOE experiments (Scheme 7).

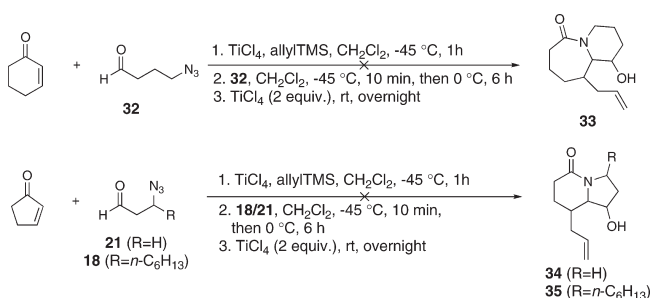
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SCHEME 7



SCHEME 8



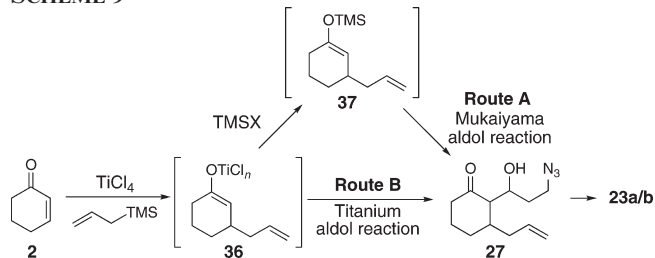
The analogous reaction was attempted with the homoalog aldehyde substrate, 4-azidobutanal (**32**)²⁰ (Scheme 8). We had previously shown that the intramolecular Schmidt reaction involving a 7-membered azidohydrin intermediate is possible under strong Lewis acid conditions although less favorable than those that entail a 6-membered intermediate.³ In the present instance, the resulting aldol product from 4-azidobutanal and enone **2** under strong acidic conditions resulted in complex mixture without any sight of the desired Schmidt product **33**. Presumably, various side reactions prevailed before the Schmidt reaction occurred.

Reactions of 2-cyclopenten-1-one were also attempted with 3-azidoaldehyde **18** and **21**, neither of which generated the desired domino products **34** or **35**. Only the 1,4-allylated Sakurai product of 2-cyclopenten-1-one was observed in the crude reaction mixtures, suggesting that the aldol reaction did not proceed in either case. As previously reported by Kuwajima,¹² the titanium enolate generated from cyclopentanone was found to be unstable, possibly explaining the absence of the desired products.

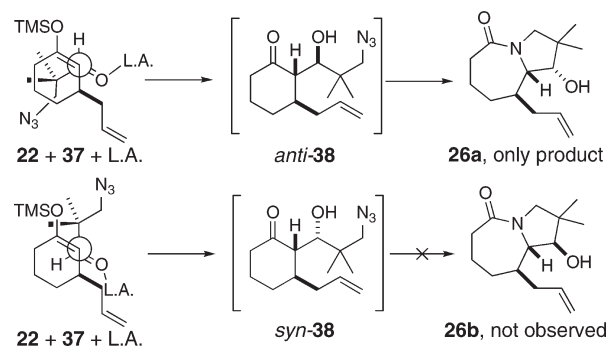
Unusual *Anti*-Aldol Selectivity of Domino Sakurai–Aldol–Schmidt Reaction. To understand the *anti*-aldol selectivity of the Sakurai/aldol/Schmidt reaction, we sought a possible mechanism of this reaction. We initially considered the silyl enol ether **37** formed from TMSCl and the titanium enolate **36** generated from the Sakurai reaction as a potential reaction intermediate (Scheme 9, route A).

An open transition-state model for the Mukaiyama aldol reaction could explain the observed *anti* selectivity of our

SCHEME 9



SCHEME 10



aldol reaction products. However, this model fails to explain the high *anti* stereoselectivity of bulky aldehyde **22** (Scheme 10). The sole formation of **26a** would require the dominating intermediacy of *anti*-**38**, which does not appear to be greatly favored because of the steric interaction between bulky aldehyde side chain and cyclohexene ring, relative to the alternative *syn*-**38**, leading to **26b** (not observed). In contrast to these results, Barner observed the inversion of stereoselectivity from *anti* to *syn* in Mukaiyama aldol reaction of pulegone with bulky aldehydes, which is inconsistent with the observed increase of *anti*-selectivity obtained with increasing bulk from **21** to **22**.²¹ Our results therefore suggest that the domino Sakurai/aldol/Schmidt reaction does not involve a Mukaiyama-type aldol reaction and an open transition state.

The major diastereomer **23a** of the domino Sakurai/aldol/Schmidt reaction could also arise from the corresponding titanium aldol intermediate **39a** or **39b** (Scheme 11). The same *anti* selectivity of the aldol reaction was also observed previously in the titanium aldol/Schmidt reaction product lactam **19** (see Scheme 4), which strongly suggests that these aldol reaction components involve a titanium enolate (Scheme 9, route B). In general, the stereochemical outcome of aldol reactions involving titanium enolates is *syn* regardless of the enolate geometry.¹³ Thus, (*Z*)-titanium enolates have been proposed to react with aldehydes via chairlike transition states to furnish *syn*-aldol products,²² whereas (*E*)-titanium enolates are believed to utilize boatlike transition states^{23,24} similar to **39c** to also generate *syn* products.^{14,25}

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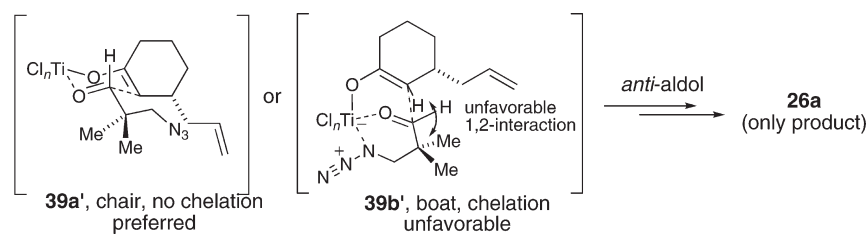
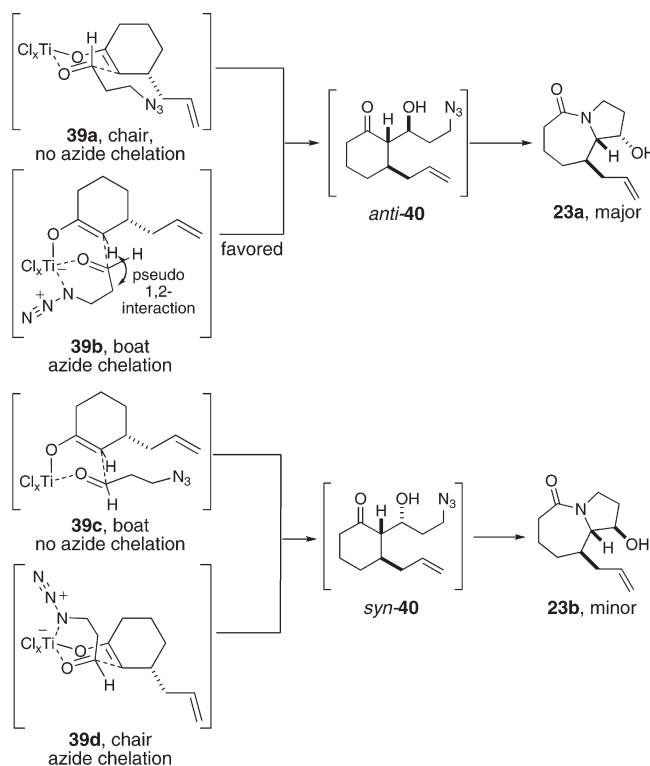


FIGURE 1. Two possible transition states for 2,2-dimethyl-3-propanal (**22**).

SCHEME 11



We considered two possible explanations to account for the observed *anti*-selectivity. The first possibility includes the formation of a chairlike Zimmerman–Traxler transition state²⁶ **39a** instead of a boatlike transition state **39c**. However, there is no clear reason why 3-azido-containing aldehydes would prefer a chairlike transition state **39a** with (*E*)-titanium enolate while all of the available precedents^{14,23–25,27,28} suggest a boatlike transition state **39c** as being preferred under similar conditions. However, a corresponding chairlike transition state **39a'** could plausibly explain the high stereoselectivity observed with bulky aldehyde **22**, which led to the exclusive formation of *anti* product. In this case, alternative boat-transition state **39b'** would be highly unlikely because unfavorable 1,2-interactions between tertiary carbon on the aldehyde and α -proton or

cyclohexyl moiety of the enolate would be an extremely destabilizing factor (Figure 1).

A second possibility invokes a chelation model **39b** where the titanium is coordinated to both the carbonyl group and an azide nitrogen atom. In spite of the low basicity of sp^2 nitrogen atoms, it is known that azide groups can participate in chelation. Kihlberg proposed chelation of an azide nitrogen with an acetal oxygen via a Lewis acidic silicon atom and supported this idea with a ^{15}N NMR experiment.²⁹ Shimizu proposed a chelated half-chair transition state to explain *anti*-1,3-stereoselectivities in nucleophilic addition to a 3-azidoimine.^{30,31} Thus, intermediacy of chelate **39b** could plausibly explain the observed *anti*-selectivity of our aldol reaction. It is unclear if such chelation could compensate for an unfavorable pseudodiaxial interaction between an α -hydrogen of the enolate reaction partner and the α -methylene group of the aldehyde in the boat-like transition state, which would instead favor alternative boatlike transition state **39c** leading to minor aldol intermediate *syn*-**40**.²⁴ However, such interactions seems to depend on the situation. For example, Hoppe accounted for a stereoselective titanium enolate addition by proposing a boat transition state in which a methyl and tosylamine group were both placed in 1,2-dipseudoaxial positions.²⁸

If the transition state **39b** is responsible for the stereochemical outcome of the present reaction, the same type of chelate-controlled aldol reaction of (*E*)-titanium enolate with other nonazide-containing but chelatable aldehydes such as 3-benzyloxypropionaldehyde (**41**) should be also possible. We tested this hypothesis by performing an aldol reaction of titanium enolate **17** with 3-benzyloxypropionaldehyde (**41**). Titanium enolate **17** was generated by treating cyclohexanone with TiCl_4 followed by *i*- Pr_2EtN .²² The resulting **17** was treated with aldehyde **41** to obtain aldol product **42** as a mixture of two diastereomers (*anti*/*syn* = 1.8:1) in 46% yield (Scheme 12). Initial attempts at stereospecific assignment of the NMR spectrum focused on measuring the $^3J(\text{H}_\alpha\text{--H}_\beta)$ coupling constant to assess the dihedral angle using the Karplus curve (Stiles–House method).³² Unfortunately, we could not measure $^3J(\text{H}_\alpha\text{--H}_\beta)$ by selective

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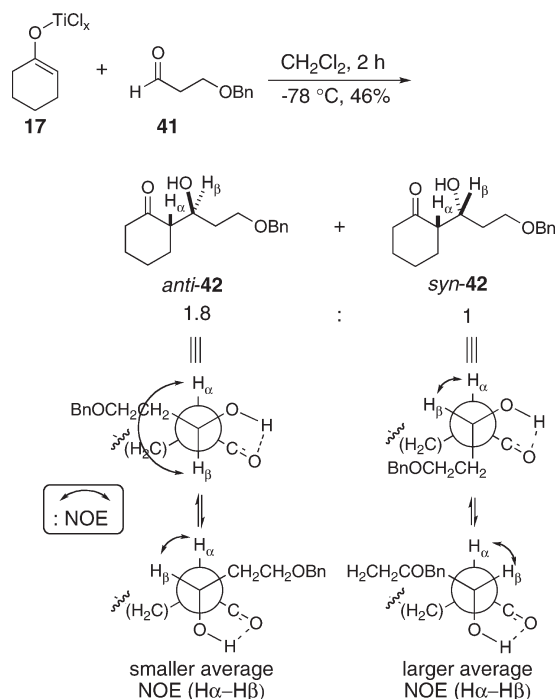
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SCHEME 12

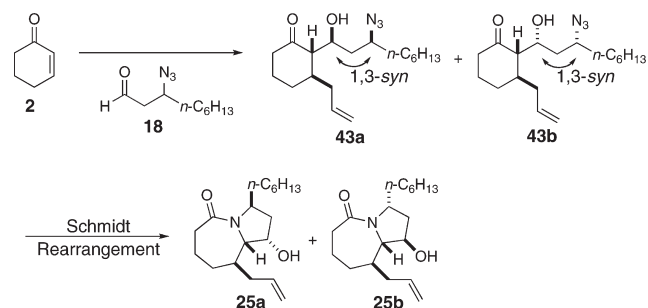


homonuclear decoupling because of overlapping of the peaks and the complex splitting patterns in the decoupled 1D ^1H spectrum. Alternatively, the E-COSY experiment³³ was recorded and analyzed for **42**. However, the presence of multiple passive coupling led to complex cross-peak patterns, which did not yield conclusive $^3J(\text{H}_\alpha\text{--H}_\beta)$ values. These complications motivated us to use NOE-based approach to assign the diastereomers through interproton distances. The initial slope of the NOE buildup curves measured via a GOESY (gradient enhanced NOE spectroscopy) experiment³⁴ enabled us to assign the major product as *anti*-**42** (for details, see the Supporting Information). The moderate level of diastereoselectivity from the titanium aldol reaction between cyclohexanone and **42** showed that chelation control is still possible even with an unfavorable 1,2-diaxial-like interaction in the proposed boat transition state analogous to **39b**. This experiment also provides indirect evidence that our 3-azido-aldehyde substrates could react with the titanium enolate of cyclohexanone via chelated boat transition state **39b**.

Unusual 1,3-Syn-Selectivity in the Aldol Reaction of 3-Azidononanal (18). Another unexpected stereochemical outcome was observed in the reaction between 3-azidononanal **18** and enone **2**. Specifically, the aldol products **43a** and **43b** were formed with unusually high 1,3-*syn*-stereoselectivity, which was the sole relative stereochemistry observed in both products isolated from this reaction (Scheme 13).

There are two widely accepted models for 1,3-asymmetric induction in the nucleophilic addition to β -heteroatom-substituted aldehydes. Those are the Retz chelation model³⁵ and

SCHEME 13



Evans nonchelating dipole interaction model.³⁶ However, both analyses predict the formation of 1,3-*anti* products. To the best of our knowledge, this aldol reaction with aldehyde **18** is a very rare example of 1,3-*syn* asymmetric induction.³⁷ However, the origin of this 1,3-*syn* selectivity is unclear in this point and the subject of further investigation in our laboratory.

Experimental Section

General Procedures. All reaction solvents were purified before use. Tetrahydrofuran, dichloromethane, and diethyl ether were purified by passing through a solvent column composed of activated A-1 alumina. Unless indicated otherwise, all reactions were conducted under an atmosphere of nitrogen or argon using flame-dried glassware. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a commercial 400 MHz instrument. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. The proton signal for residual nondeuterated solvent (δ 7.26³⁸ for CHCl_3) was used as an internal reference for ^1H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.0 resonance of CDCl_3 . Coupling constants are reported in hertz.

1-(3-Allylpyrrolidin-1-yl)ethanone (9). To a solution of **6**⁵ (68 mg, 0.49 mmol) in CH_2Cl_2 (0.3 M with respect to **6**) at -78 °C were added titanium tetrachloride (2 equiv) and allyltrimethylsilane (2 equiv). The solution was stirred at -78 °C for 3 h and allowed to warm to 0 °C over 5 h. MeOH (5 equiv) was added, and the solution was stirred at room temperature for 45 min. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride and extracted with CH_2Cl_2 . The organic layer was washed with brine and aqueous saturated NaHCO_3 solution. On evaporation and purification of the organic layer by chromatography, the oily product **9** was obtained as a mixture of rotamers (35 mg, 47%): IR (neat) 3460, 1610, 1610 cm^{-1} ; HRMS-ESI (m/z) [$\text{M} + \text{H}^+$] calcd for $\text{C}_9\text{H}_{16}\text{NO}^+$ 154.1232, found 154.1380; major rotamer ^1H NMR (400 MHz, CDCl_3) δ 1.59–1.69 (m, 1H), 1.92–2.40 (m, 4H), 2.02, (s, 3H), 2.96–3.11 (m, 1H), 3.28–3.45 (m, 1H), 3.46–3.75 (m, 2H), 4.95–5.15 (m, 2H), 5.67–5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 31.6, 37.2, 38.9, 47.0, 52.3, 116.4, 136.0, 169.3; minor rotamer (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 22.4, 30.2, 37.2, 37.4, 45.1, 50.2, 116.6, 136.1, 169.3.

(9*R,9*aS**)-9-Allylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (14).** To a solution of azido enone **10** (58 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) at -78 °C were added TiCl_4 (0.12 mg, 0.65 mmol) and allyltrimethylsilane (0.10 mL, 0.65 mmol).

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(37) For an example of 1,3-*syn*-stereoselective aldol reaction under non-chelating conditions, see: Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, 128, 48–49.

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The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h and allowed to come to $0\text{ }^{\circ}\text{C}$ over 5 h. *t*-BuOH (0.15 mL, 1.6 mmol) was added, and the solution was stirred at room temperature for 45 min. The reaction mixture was then quenched by the addition of a saturated solution of ammonium chloride and extracted with CH_2Cl_2 . The organic layer was washed with brine and aqueous saturated sodium bicarbonate solution. Upon evaporation and purification of the organic layer by chromatography (SiO_2 , 5% MeOH in CH_2Cl_2), a mixture of two diastereomeric products **14** was obtained as an oil (49 mg, 79%, dr > 9:1): HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{20}\text{NO} [\text{M} + \text{H}^+]$ 194.1545, found 194.1570. Major diastereomer **14a**: oil; IR (neat) 2940, 1630 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.40–2.69 (m, 13H), 3.16–3.29 (m, 1H), 3.80–3.92 (m, 1H), 3.98–4.09 (m, 1H), 4.99–5.14 (m, 2H), 5.64–5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.5, 23.7, 28.9, 31.6, 32.4, 37.9, 40.0, 47.5, 61.4, 116.6, 136.7, 173.9. Minor diastereomer **14b**: oil; IR (neat) 2920, 1630 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.12–2.67 (m, 13H), 3.21–3.36 (m, 1H), 3.48–3.61 (m, 1H), 3.80–3.95 (m, 1H), 5.02–5.15 (m, 2H), 5.64–5.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 23.1, 28.9, 32.5, 34.6, 37.6, 42.2, 62.9, 62.6, 117.1, 135.6, 174.7.

(8*R,8*aS**)-8-Allylhexahydroindolizin-5(1*H*)-one (15a) and (8*R**,8*aR**)-8-Allylhexahydroindolizin-5(1*H*)-one (15b)**. To a solution of azido enone **11** (144 mg, 0.87 mmol) in CH_2Cl_2 (3 mL) at $-78\text{ }^{\circ}\text{C}$ were added titanium tetrachloride (0.24 mL, 1.75 mmol) and allyltrimethylsilane (0.28 mL, 1.75 mmol). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h and allowed to come to $0\text{ }^{\circ}\text{C}$ over 5 h. *tert*-Butyl alcohol (0.41 mL, 4.4 mmol) was added, and the solution was stirred at room temperature for 45 min. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride and extracted with CH_2Cl_2 . The organic layer was washed with brine and aqueous saturated sodium bicarbonate solution. On evaporation and purification of the organic layer by chromatography (SiO_2 , 5% MeOH in CH_2Cl_2), a mixture of two diastereomeric products **15** was afforded as an oil (78 mg, 50%, dr = 64:36). Major diastereomer **15a**: oil; IR (neat) 2940, 1610, 1410 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{NO} [\text{M} + \text{H}^+]$ 180.1388, found 180.1360; ^1H NMR (400 MHz, CDCl_3) δ 1.60–2.08 (m, 7H), 2.09–2.63 (m, 4H), 3.45–3.63 (m, 2H), 3.64–3.77 (m, 1H), 5.06–5.18 (m, 2H), 5.69–5.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 24.1, 26.2, 28.7, 29.5, 32.9, 45.5, 62.3, 117.1, 135.6, 170.5. Minor diastereomer **15b**: oil; IR (neat) 2920, 1610, 1410 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{NO} [\text{M} + \text{H}^+]$ 180.1388, found 180.1369; ^1H NMR (400 MHz, CDCl_3) δ 1.36–2.68 (m, 11H), 3.06–3.24 (m, 1H), 3.44–3.70 (m, 2H), 5.03–5.22 (m, 2H), 5.69–5.88 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.1, 26.3, 30.5, 32.1, 36.9, 39.8, 45.6, 63.8, 117.5, 134.9, 170.5.

(8*R,8*aR**)-8-Allylhexahydroindolizin-5(1*H*)-one (15b)**. To a solution of azidoenone **11** (144 mg, 0.87 mmol) in CH_2Cl_2 (3 mL) at $-78\text{ }^{\circ}\text{C}$ were added titanium tetrachloride (0.24 mL, 1.75 mmol) and allyltrimethylsilane (0.28 mL, 1.75 mmol). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h before quenching with aqueous saturated NH_4Cl solution. The biphasic mixture was warmed to rt. The organic layer was extracted with 50 mL ether and washed with aqueous saturated NaHCO_3 solution and brine. The solution was dried over Na_2SO_4 , filtered, and concentrated. The resulting crude residue was dissolved in 0.9 mL of trifluoroacetic acid. The resulting mixture was stirred at rt for 30 min. The reaction mixture was diluted with 50 mL of ether and quenched carefully with aqueous saturated NaHCO_3 . The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude oil residue was purified by column chromatography (SiO_2 , 5% MeOH in CH_2Cl_2) to afford **15b** as an oil (74 mg, 47%).

(1*S,3*S**,9*aS**)-3-Hexyl-1-hydroxyhexahydro-1*H*-pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (19)**. To a stirred solution of TiCl_4 (0.11

mL, 1.0 mmol) in 5 mL of CH_2Cl_2 was added cyclohexenyloxytrimethylsilane (**16**) dropwise at ambient temperature. The resulting mixture was stirred for 2 min and then cooled to $-45\text{ }^{\circ}\text{C}$ (acetonitrile–dry ice bath). A solution of 3-azidononanal (**18**, 210 mg, 1.1 mmol) in 0.6 mL of CH_2Cl_2 was added slowly to the in situ generated titanium enolate solution. The reaction mixture was stirred at $-45\text{ }^{\circ}\text{C}$ for 10 min and rt for 24 h. After being quenched with 20 mL of aqueous saturated NH_4Cl solution, the organic layer was extracted with CH_2Cl_2 (20 mL \times 3), and the combined extracts were dried over Na_2SO_4 , filtered, and concentrated to afford crude product. The crude product was purified by column chromatography (SiO_2 , 5% MeOH– CH_2Cl_2) to afford **19** (135 mg, 53%) as a mixture of four diastereomers (major/sum of all minors = 56:44). From further purification with column chromatography and recrystallization from THF, a pure major diastereomer could be obtained: mp 122–124 $^{\circ}\text{C}$; IR (thin layer) 1618 cm^{-1} ; HRMS-ESI (m/z) [$\text{M} + \text{H}^+$] calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_2$ 254.2115, found 254.2097. Major diastereomer: mp 122–124 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 0.82–0.87 (m, 3H), 1.10–1.34 (m, 10H), 1.43–1.58 (m, 2H), 1.80–1.89 (m, 3H), 1.95 (ddd, $J = 12.4$, 6.4, 1.6 Hz, 1H), 1.99–2.04 (m, 1H), 2.05–2.10 (m, 1H), 2.43–2.46 (m, 2H), 3.76 (dd, $J = 10.8$, 7.2 Hz, 1H), 3.96–4.01 (m, 1H), 4.47 (dt, $J = 10.4$, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.6, 23.5, 26.4, 27.0, 29.0, 29.2, 31.8, 33.8, 35.0, 38.1, 55.2, 61.7, 70.5, 174.4. Minor diastereomers (diagnostic peaks correspond to the 3.76 ppm peak of the major diastereomer): ^1H NMR (400 MHz, CDCl_3) 3.72 (d, $J = 10.4$ Hz, 1H, first minor diastereomer), 3.40 (dd, $J = 10.4$, 6.4 Hz, 1H, second minor diastereomer), 3.18–3.22 (m, 1H, third minor diastereomer).

General Conditions A for Domino Sakurai/Aldol/Schmidt Reaction for Azido-Containing Aldehyde Substrates. To a solution of enone (1.0 mmol) in 5 mL of CH_2Cl_2 was added TiCl_4 (0.11 mL, 1.0 mmol) followed by allyltrimethylsilane (0.22 mL, 1.4 mmol) dropwise at $-45\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere. The resulting deep red solution was stirred for 1 h at $-45\text{ }^{\circ}\text{C}$. To this reaction solution was added slowly the azidoaldehyde (1.6 mmol) dissolved in 1 mL of CH_2Cl_2 over a 3 min period. After being stirred at $-45\text{ }^{\circ}\text{C}$ for 10 min, the reaction flask was disconnected from nitrogen source, wrapped with parafilm, and kept in a $0\text{ }^{\circ}\text{C}$ refrigerator for 24 h without stirring. The flask was brought out to place in an ice bath. Upon stirring, the reaction was quenched with aqueous saturated NH_4Cl solution (50 mL), and the aqueous layer was extracted three times with CH_2Cl_2 (3 \times 50 mL). The combined CH_2Cl_2 solution was dried over Na_2SO_4 , filtered, and concentrated. The resulting crude material was purified by column chromatography (SiO_2 , 10% MeOH/ CH_2Cl_2) to afford the corresponding lactam products.

General Conditions B for Domino Sakurai/Aldol/Schmidt Reaction. The same procedure as A was followed up to the point where the reaction flask was placed in a $0\text{ }^{\circ}\text{C}$ refrigerator. Then, the reaction flask was kept for only 6 h in the refrigerator instead of 24 h. Upon stirring at $0\text{ }^{\circ}\text{C}$ under nitrogen atmosphere, an additional 2 equiv of TiCl_4 (0.22 mL, 0.2 mmol) was added, which resulted in gentle bubbling. After the bubbling subsided, the reaction flask was again kept in a $0\text{ }^{\circ}\text{C}$ refrigerator for 18 h. The workup procedure was initiated by quenching with aqueous saturated NH_4Cl and was thereafter identical to the general procedure A.

(1*S,9*R**,9*aS**)-9-Allyl-1-hydroxyhexahydro-1*H*-pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (23a)**. Compound **23** was prepared from 2-cyclohexen-1-one (**12**, 0.10 mL, 0.10 mmol) and 3-azidopropionaldehyde (**21**, 160 mg, 1.6 mmol) using either general conditions A or general conditions B. After column purification, 79 mg of **23a/b** was obtained as a solid mixture of two diastereomers (ratio = 6.4:1) by following conditions A or 123 mg of **23a/b** as an oily mixture of three diastereomers (ratio = 2.6:1) by

following the conditions B. The structure of the major diastereomer **23a** was determined by X-ray crystallography after recrystallization from MeOH/EtOAc: mp 171–172°C; IR (neat) 3250, 1610 cm⁻¹; HRMS calcd for C₁₂H₂₀NO₂ [M + H⁺] 210.1494, found 210.1508. Major diastereomer **23a**: ¹H NMR (400 MHz, CDCl₃) δ 1.31–1.44 (m, 1H), 1.45–1.62 (m, 1H), 1.73–1.82 (m, 2H), 1.84–1.96 (m, 3H), 2.10 (dt, *J* = 15.2, 8.0 Hz, 1H), 2.33–2.25 (m, 1H), 2.47–2.41 (m, 1H), 2.54 (ddd, *J* = 14.4, 6.8, 2.4 Hz, 1H), 3.41 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.51 (td, *J* = 11.2, 6.0 Hz, 1H), 3.94 (ddd, *J* = 11.6, 8.0, 2.0 Hz, 1H), 4.53 (dd, *J* = dd, *J* = 6.0, 4.0 Hz, 1H), 5.08–5.02 (m, 2H), 5.86–5.72 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.2, 32.1, 33.6, 36.7, 37.3, 38.0, 45.3, 66.6, 72.7, 116.7, 136.4, 174.6. Minor diastereomer **23b**: ¹H NMR (400 MHz, CDCl₃, diagnostic peaks only from the mixture) 3.69 (ddd, *J* = 12.0, 9.2, 7.2 Hz, 1H), 4.41 (m, 1H) ppm.

2-(1-Azidohept-5-en-3-yl)cyclohex-2-enone (24). Isolated as a side product from the reaction described above, following conditions A: IR (neat) 2924, 2096, 1674, 1456 cm⁻¹; HRMS calcd for C₁₂H₁₈NO [M - N₂ + H⁺] 192.1383, found 192.1369. ¹H NMR (400 MHz, CDCl₃) δ 1.71–1.81 (m, 2H), 1.93–2.00 (m, 2H), 2.15–2.27 (m, 2H), 2.37–2.44 (m, 4H), 2.76 (apparent quint, *J* = 7.2 Hz, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 4.93–4.95 (m, 1H), 4.97 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.58–5.69 (m, 1H), 6.69 (t, *J* = 4.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.8, 26.1, 32.4, 36.1, 38.6, 38.8, 49.7, 116.4, 136.4, 140.7, 145.7, 198.9.

(1*S, 3*S**, 9*R**, 9*aS**)-9-Allyl-3-hexyl-1-hydroxyhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (25a)**. Prepared from 2-cyclohexen-1-one (**12**, 0.10 mL, 0.10 mmol) and 3-azidononanal (**18**, 290 mg, 1.6 mmol) using either general conditions A or general conditions B. After purification with column chromatography, 101 mg (34%) of **25a/b** was obtained as a solid mixture of two diastereomers (ratio = 4.2:1) by following the general conditions A or 173 mg (59%) of **25a/b** as a solid mixture of four diastereomers (ratio between major and sum of all other minor diastereomer = 1.8:1) by following the general conditions B. The structure of the major diastereomer **25a** was determined by X-ray crystallography after recrystallization from MeOH/EtOAc: mp 96–98 °C; IR (neat) 1614 cm⁻¹; HRMS calcd for C₁₈H₃₂NO₂ [M + H⁺] 294.2428, found 294.2426. Major diastereomer **25a**: ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.25 (m, 9H), 1.49–1.58 (m, 2H), 1.66–1.72 (m, 2H), 1.76 (dt, *J* = 13.2, 6.0 Hz, 1H), 1.88–1.97 (m, 2H), 2.00–2.12 (m, 2H), 2.31–2.50 (m, 3H), 3.40 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.13 (m, 1H), 4.42 (dd, *J* = 10.8, 5.2 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 17.2 Hz, 1H), 5.72–5.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 18.3, 22.6, 25.7, 28.1, 29.2, 31.9, 33.6, 34.0, 34.8, 36.3, 37.0, 55.8, 65.5, 71.3, 116.7, 136.5, 173.3. Minor diastereomer **25b**: ¹H NMR (400 MHz, CDCl₃) 0.86 (t, *J* = 6.8 Hz, 3H), 1.33 (m, 9H), 1.37–1.57 (m, 3H), 1.79–1.97 (m, 5H), 2.03–2.11 (m, 1H), 2.34–2.46 (m, 3H), 3.35 (dd, *J* = 9.6, 4.4 Hz), 4.20 (m, 1H), 4.43 (dd, *J* = 10.8, 6.4 Hz, 1H), 5.04–5.11 (m, 2H), 5.76–5.83 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 14.0, 21.8, 22.6, 26.3, 29.3, 31.8, 34.3, 34.5, 36.9, 37.1, 37.5, 41.9, 56.2, 70.3, 74.6, 116.9, 136.4, 173.8.

(1*S, 9*R**, 9*aS**)-9-Allyl-1-hydroxy-2,2-dimethylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (26a)**. Prepared from 2-cyclohexen-1-one (**2**, 0.10 mL, 0.10 mmol) and 3-azido-2,2-dimethylpropanal (**22**, 290 mg, 1.6 mmol) using either general conditions A or general conditions B. After purification with column chromatography, 100 mg (42%) of **26a** was obtained as

a solid single diastereomer by following general conditions A or 133 mg (56%) of **26a** as a solid single product by following general conditions B. The structure of the **26a** was determined by X-ray crystallography after recrystallization from tetrahydrofuran: mp 154–155 °C; IR (thin layer) 3282 (br), 2916, 1606 cm⁻¹; HRMS calcd for C₁₄H₂₄NO₂ [M + H⁺] 238.1807, found 238.1792; ¹H NMR (400 MHz, CDCl₃) δ 0.92 (s, 3H), 1.08 (s, 3H), 1.32 (tdd, *J* = 14.0, 10.8, 3.2 Hz, 1H), 1.45–1.56 (m, 1H), 1.74–1.82 (m, 1H), 1.85–1.92 (m, 1H), 1.99–2.08 (m, 2H), 2.28 (ddd, *J* = 14.8, 12.0, 2.8 Hz, 1H), 2.38–2.44 (m, 1H), 2.57 (dd, *J* = 6.0 Hz, 14.4 Hz, 1H), 3.23 (d, *J* = 11.2 Hz, 1H), 3.62 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.83 (t, *J* = 4.4 Hz, 1H), 5.04–5.09 (m, 2H), 5.75–5.85 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 19.9, 21.5, 24.4, 34.3, 36.7, 37.3, 38.0, 39.4, 56.4, 65.6, 79.5, 116.4, 136.5, 175.0.

(*S)-2-((*S**)-3-(Benzyloxy)-1-hydroxypropyl)cyclohexanone (anti-42) and (*S**)-2-((*R**)-3-(Benzyloxy)-1-hydroxypropyl)cyclohexanone (syn-42)**. The Evans protocol for titanium aldol reaction was followed.²⁴ To a solution of cyclohexanone (0.35 mL, 3.4 mmol) in CH₂Cl₂ (17 mL) was added TiCl₄ (0.40 mL, 3.6 mmol) as a neat solution dropwise at -78 °C. Three minutes later, *i*-Pr₂EtN (0.68 mL, 3.9 mmol) was added to the resulting pale yellow solution which resulted in a gradual color change to dark red. The reaction mixture was then stirred at -78 °C for 1 h to ensure the formation of the titanium enolate. A solution of 3-benzyloxypropionaldehyde (**41**, 0.46 g, 2.8 mmol) in CH₂Cl₂ (2.8 mL) was then added slowly over 5 min. After the addition of aldehyde, the reaction mixture was stirred at -78 °C for 2 h before quenching with aqueous saturated NH₄Cl solution (20 mL). After being warmed to rt, the reaction mixture was diluted with 50 mL of ether. The organic layer was separated and washed successively with aqueous saturated NaHCO₃ solution (30 mL) and brine (30 mL) and then dried over Na₂SO₄, filtered, and concentrated to afford crude mixture. NMR analysis on the resulting crude mixture showed a diastereomeric ratio of 1.8:1. The resulting crude mixture was purified by column chromatography (SiO₂, 33% EtOAc in hexanes) to afford **42** (316 mg, 46%) as an inseparable mixture of two diastereomers: IR (thin layer) 3507, 2932, 2859, 1702, 1451, 1100 cm⁻¹; HRMS calcd for C₁₆H₂₂NaO₃ [M + H⁺] 285.1461, found 285.1440. ¹H NMR (400 MHz, CDCl₃) δ 1.36–1.86 (m, 7H), 1.95–2.02 (m, 1H), 2.04–2.11 (m, 1H), 2.18–2.38 (m, 3H), 2.94 (d, *J* = 3.6 Hz, 0.3H, *syn*-**42**), 3.49 (d, *J* = 4.0 Hz, 0.7H, *anti*-**42**), 3.57–3.60 (m, 0.6H, *syn*-**42**), 3.62 (t, *J* = 6.4 Hz, 1.4H, *anti*-**42**), 3.91 (dddd, *J* = 9.2, 6.8, 4.0, 2.8 Hz, 0.7H, *anti*-**42**), 4.19 (dddd, *J* = 9.2, 3.6, 3.6, 3.6 Hz, 0.3H, *syn*-**42**), 4.44 (s, 0.6H, *syn*-**42**), 4.45 (s, 1.4H, *anti*-**42**), 7.19–7.29 (m, 5H) ppm.

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Supporting Information Available: Experimental details and characterization data for substrates **10** and **11** and their synthetic intermediates, ¹H/¹³C NMR spectra for new compounds, and X-ray data for compounds **19** (major), **23a**, **25a**, and **26a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.