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

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Abstract

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.

Keywords
Schmidt reaction; lactam synthesis; azides; domino reaction; Sakurai reaction; stereoselective aldol reaction; titanium enolate; GOESY

Introduction

Domino reactions, in which two or more reactions are carried out sequentially in one pot, have the potential of increasing efficiency over traditional multi-step processes. Our continuing efforts to explore the Lewis acid-promoted reaction of alkyl azides 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 domino Diels–Alder/ intramolecular Schmidt reaction and described its use in natural product and library synthesis.
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 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 context. Other laboratories have also begun to examine the utilization of the Schmidt reaction in a domino reaction context.

A logical next step was to study the combination of other Lewis acid promoted reactions with the intramolecular Schmidt reaction. For example, the Sakurai and aldol reaction are typically mediated by Lewis acids similar to those used in the intramolecular Schmidt rearrangement. Furthermore, both the Sakurai reaction/protonation of 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. Reaction of 6 with allyltrimethylsilane in the presence of TiCl4 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 TiCl4 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 TiCl4, is acidic enough to mediate the subsequent intramolecular Schmidt reaction to give lactam 9 in 46% yield.

We also prepared and tested azide-containing cyclic enone substrates 10 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-butanol, respectively. The improved selectivity with bulky tert-butanol 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 attack from the alternate conformation 12. 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 an saturated NH4Cl solution followed by treatment with TFA resulted in the exclusive formation of thermodynamic 15b in overall 47% 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 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 TiCl₄ in the presence of an aldehyde should enact a Mukaiyama aldol reaction. In contrast, aging a solution of 16 and TiCl₄ leads to titanium enolate 17 via transmetalation. While silyl enol ether 16 is expected to react via an open transition state, 17 should go via a closed transition state. 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, no reaction combining a Sakurai reaction, an aldol reaction, and Schmidt reaction has been reported.

Several 3-azidoaldehydes such as 18, 21, 22 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 TiCl₄ in CH₂Cl₂ at −45 °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 °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). In these conditions, aldol reaction did not occur unless the reaction mixture was warmed to 0 °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. SnCl₄, BF₃•OEt₂, MeAlCl₂), 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 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-azidononanal (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 °C and could be complicated by decomposition pathways at that temperature. Therefore, the procedure was modified by adding 2 additional equiv of TiCl₄ at 0 °C to facilitate the rapid completion of the Schmidt reaction (conditions B, Scheme 5). Upon addition of TiCl₄, 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 °C overnight (Conditions B in Scheme 5). Using this 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. 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 precededent 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).

The analogous reaction was attempted with the homologous 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 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 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 \textit{anti} to \textit{syn} in Mukaiyama aldol reaction of pulegone with bulky aldehydes, which is inconsistent with the observed increase of \textit{anti}-selectivity obtained with increasing bulk from 21 to 22.\textsuperscript{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 \textit{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 \textit{syn} regardless of the enolate geometry.\textsuperscript{13} Thus, (Z)-titanium enolates have been proposed to react with aldehydes via chair-like transition states to furnish \textit{syn}-aldol products,\textsuperscript{22} whereas (E)-titanium enolates are believed to utilize boat-like transition states\textsuperscript{23,24} similar to 39c to also generate \textit{syn} products.\textsuperscript{14,25}

We considered two possible explanations to account for the observed \textit{anti}-selectivity. The first possibility includes the formation of a chair-like Zimmerman–Traxler transition state\textsuperscript{26} 39a instead of a boat-like transition state 39c. However, there is no clear reason why 3-azido-containing aldehydes would prefer a chair-like transition state 39a with (E)-titanium enolate while all of the available precedents\textsuperscript{14,23–25,27,28} suggests a boat-like transition state 39c as being preferred under similar conditions. However, a corresponding chair-like transition state 39a could plausibly explaining the high stereoselectivity observed with bulky aldehyde 22, which led to the exclusive formation of \textit{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 wherein the titanium is coordinated to both the carbonyl group and an azide nitrogen atom. In spite of the low basicity of sp\textsuperscript{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 \textsuperscript{15}N NMR experiment.\textsuperscript{29} Shimizu proposed a chelated half-chair transition state to explain \textit{anti}-1,3-stereoselectivities in nucleophilic addition to a 3-azidoimine.\textsuperscript{30,31} Thus, intermediacy of chelate 39b could plausibly explain the observed \textit{anti}-selectivity of our aldol reaction. It is unclear if such chelation could compensate for an unfavorable pseudo-diaxial 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 boat-like transition state 39c leading to minor aldol intermediate \textit{syn}-40.\textsuperscript{24} However, such interaction 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-di-pseudoaxial positions.\textsuperscript{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 non-azido-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\textsubscript{4} followed by i-Pr\textsubscript{2}EtN.\textsuperscript{22} The resulting 17 was treated with aldehyde 41 to obtain aldol product 42 as a mixture of two diastereomers (\textit{anti}: \textit{syn} = 1.8 : 1) in 46% yield (Scheme 12). Initial attempts at stereospecific assignment of the NMR spectrum focused on measuring the \textit{J}(H\textsubscript{α}–H\textsubscript{β}) coupling constant to assess the dihedral angle using the Karplus curve (Stiles-House Method).\textsuperscript{32} Unfortunately, we could not measure \textit{J}(H\textsubscript{α}–H\textsubscript{β}) by selective
homonuclear decoupling because of overlapping of the peaks and the complex splitting patterns in the decoupled 1D $^1$H spectrum. Alternatively, the E-COSY experiment was recorded and analyzed for 42. However, the presence of multiple passive coupling led to complex cross-peak patterns, which did not yield conclusive $^3J$(Hα–Hβ) values. These complications motivated us to use NOE-based approach to assign the diastereomers through inter-proton distances. The initial slope of the NOE buildup curves measured via a GOESY (gradient enhanced NOE spectroscopy) experiment enabled us to assign the major product as anti-42 (for details, see 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-azidoaldehyde substrates could react with the titanium enolate of cyclohexanone via chelated boat transition state 39b.

**Unusual 1,3-syn-selectivity in 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 Reetz chelation model and Evans non-chelating dipole interaction model. However, both analyses predict the formation of 1,3-anti products. To the best of our knowledge, this aldol reaction with aldehyde 18 is very rare example of 1,3-syn asymmetric induction. 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 ($^1$H 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 non-deuterated solvent (δ 7.26 for CHCl$_3$) was used as an internal reference for $^1$H 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 Hz.

1-(3-Allylpyrrolidin-1-yl)ethanone (9)

To a solution of 6 (68 mg, 0.49 mmol) in CH$_2$Cl$_2$ (0.3 M with respect to 6) at −78 °C was added titanium tetrachloride (2 equiv) and allyltrimethylsilane (2 equiv). The solution was stirred at −78 °C for 3 h and allowed to come 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$_2$Cl$_2$. The organic layer was washed with brine and aq sat 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): [M +H$^+$] calcd for C$_9$H$_{16}$NO$_2^+$, 154.1232; found 154.1380; Major rotamer: $^1$H 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...
(9R*,9aS*)-9- Allylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (14)

To a solution of azido enone 10 (58 mg, 0.32 mmol) in CH$_2$Cl$_2$ (1 mL) at −78 °C was added TiCl$_4$ (0.12 mL, 0.65 mmol) and allyltrimethylsilane (0.10 mL, 0.65 mmol). The solution was stirred at −78 °C for 3 h and allowed to come to 0 °C over 5 h. t-ButOH (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$_2$Cl$_2$. The organic layer was washed with brine and aq saturated sodium bicarbonate solution. Upon evaporation and purification of the organic layer by chromatography (SiO$_2$, 5% MeOH in CH$_2$Cl$_2$), a mixture of two diastereomeric product 14 was obtained as an oil (49 mg, 79%, dr >9:1). HRMS (ESI) m/z calcd for C$_{12}$H$_{20}$NO [M+H$^+$]: 194.1545 found: 194.1570; Major diastereomer (14a): oil; IR (neat) 2940, 1630 cm$^{-1}$; $^1$H 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), 5.02–5.15 (m, 2H), 5.64–5.84 (m, 1H) ppm; $^{13}$C NMR (100 MHZ, CDCl$_3$) δ 17.5, 23.7, 28.9, 31.6, 32.4, 37.9, 40.0, 47.5, 116.6, 136.7, 173.9 ppm. Minor diastereomer (14b): oil; IR (neat) 2920, 1630 cm$^{-1}$; $^1$H 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) ppm; $^{13}$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 ppm.

(8R*,8aS*)-8-Allylhexahydroindolizin-5(1H)-one (15a) and (8R*,8aR*)-8-Allylhexahydroindolizin-5(1H)-one (15b)

To a solution of azido enone 11 (144 mg, 0.87 mmol) in CH$_2$Cl$_2$ (3 mL) at −78 °C was added titanium tetrachloride (0.24 mL, 1.75 mmol) and allyltrimethylsilane (0.28 mL, 1.75 mmol). The solution was stirred at −78 °C for 3 h and allowed to come to 0 °C over 5 h. t-Butanol (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$_2$Cl$_2$. The organic layer was washed with brine and aq saturated sodium bicarbonate solution. On evaporation and purification of the organic layer by chromatography (SiO$_2$, 5% MeOH in CH$_2$Cl$_2$), 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 C$_{11}$H$_{18}$NO [M+H$^+$]: 180.1360; $^1$H 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) ppm; $^{13}$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 ppm. Minor diastereomer (15b): oil; IR (neat) 2920, 1610, 1410 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{11}$H$_{18}$NO [M+H$^+$]: 180.1388; $^1$H 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) ppm; $^{13}$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 ppm.

(8R*,8aR*)-8-Allylhexahydroindolizin-5(1H)-one (15b)

To a solution of azido enone 11 (144 mg, 0.87 mmol) in CH$_2$Cl$_2$ (3 mL) at −78 °C was added titanium tetrachloride (0.24 mL, 1.75 mmol) and allyltrimethylsilane (0.28 mL, 1.75 mmol). The solution was stirred at −78 °C for 2 h before quenching with aq saturated NH$_4$Cl solution. The biphasic mixture was warmed to rt. The organic layer was extracted with 50 mL ether, and washed with aq saturated NaHCO$_3$ solution and brine. The solution was dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting crude residue was dissolved in 0.9 mL trifluoroacetic acid. The resulting mixture was stirred at rt for 30 min. The reaction mixture was diluted with 50 mL ether and quenched carefully with aq saturated NaHCO$_3$. The organic layer was
separated, washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude oil residue was purified by column chromatography (SiO₂, 5% MeOH in CH₂Cl₂) to afford 15b as an oil (74 mg, 47%).

(1S*,3S*,9aS*)-3-Hexyl-1-hydroxyhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (19)

To a stirred solution of TiCl₄ (0.11 mL, 1.0 mmol) in 5 mL CH₂Cl₂ was added cyclohexenyloxytrimethylsilane (16) dropwise at ambient temperature. The resulting mixture was stirred for 2 min, and then cooled to −45 °C (acetonitrile–dry ice bath). A solution of 3-azidononanal (18, 210 mg, 1.1 mmol) in 0.6 mL of CH₂Cl₂ was added slowly to the in situ generated titanium enolate solution. The reaction mixture was stirred at −45 °C for 10 min and rt for 24 h. After quenching with 20 mL aq saturated NH₄Cl solution, the organic layer was extracted with CH₂Cl₂ (20 mL × 3), and the combined extracts were dried over Na₂SO₄, filtered, and concentrated to afford crude product. The crude product was purified by column chromatography (SiO₂, 5% MeOH–CH₂Cl₂) 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° IR (thin layer) 1618 cm⁻¹; HRMS–ESI (m/z): [M+H⁺] calcd for C₁₅H₂₇NO₂, 254.2115; found 254.2097. Major diastereomer: mp 122–124 °C; ¹H NMR (400 MHz, CDCl₃) 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) ppm; ¹³C NMR (100 MHz, CDCl₃) 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 ppm. Minor diastereomers (diagnostic peaks correspond to the 3.76 ppm peak of the major diastereomer): ¹H NMR (400 MHz, CDCl₃) 3.72 (d, J = 10.4 Hz, 1H, 1st minor diastereomer), 3.40 (dd, J = 10.4, 6.4 Hz, 1H, 2nd minor diastereomer), 3.40 (dd, J = 10.4, 6.4 Hz, 1H, 3rd 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 CH₂Cl₂ was added TiCl₄ (0.11 mL, 1.0 mmol) followed by allytrimethylsilane (0.22 mL, 1.4 mmol) dropwise at −45 °C under a nitrogen atmosphere. The resulting deep red solution was stirred for 1 h at −45 °C. To this reaction solution was added slowly the azidoaldehyde (1.6 mmol) dissolved in 1 mL CH₂Cl₂ over a 3 min period. After stirring at −45 °C for 10 min, the reaction flask was disconnected from nitrogen source, wrapped with parafilm, and kept in a 0 °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 aq saturated NH₄Cl solution and was thereafter identical to the general procedure A.
(1S*,9R*,9aS*)-9-Allyl-1-hydroxyhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (23a) 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 diastereomer (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°, 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 (dd, 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 (dd, 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) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 21.2, 32.1, 33.6, 36.7, 38.0, 45.3, 66.6, 72.7, 116.7, 136.4, 174.6 ppm. Minor diastereomer (23b): ¹H NMR (400 MHz, CDCl₃, diagnostic peaks only from the mixture) 3.69 (dd, J = 12.0, 9.2, 7.2 Hz, 1H), 4.41 (m, 1H) ppm.

2-(1-Azidohex-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 C₁₁H₁₇N₂O [M–N₂H⁺]: 192.1369, found 192.1383. Major diastereomer (24): 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, δ = 6.0, 4.0 Hz, 1H) 5.08–5.02 (m, 2H), 5.86–5.72 (m, 1H) ppm; 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 ppm.

(1S*,3S*,9R*,9aS*)-9-Allyl-3-hexyl-1-hydroxyhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-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 diastereomer (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°, IR (neat) 1614 cm⁻¹; HRMS calcd for C₁₈H₃₂NO₃ [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) ppm; 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 ppm. Minor diastereomer (25b): ¹H NMR (400 MHz, CDCl₃) δ 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) ppm; 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 ppm.
(1S*,9R*,9aS*)-9-Allyl-1-hydroxy-2,2-dimethylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-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°, 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) ppm; 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 ppm.

(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. 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 min 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 period. After the addition of aldehyde, the reaction mixture was stirred at −78 °C for 2 h before quenching with aq saturated NH₄Cl solution (20 mL). After warming up to rt, the reaction mixture was diluted with 50 mL of ether. The organic layer was separated and washed successively with aq 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 (dd, J = 9.2, 6.8, 4.0 Hz, 0.7H, anti-42), 4.19 (ddd, J = 9.2, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference

9. Control experiments established that related intramolecular Schmidt reactions are not promoted by Ti (Oi-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 JAC, Tabacco SA, Woerpel KA. J. Am. Chem. Soc 2000;122:168–169.
31. Although the same authors in the reference 30 also proposed no chelation formation in another paper regarding Lewis acid promoted allylation of 3-azidoaldehyde, any chelation seems unlikely under their conditions with excess water and protic acid. See Shimizu M, Nishi T. Synlett 2004:889–891.
37. For an example of 1,3-syn-stereoselective aldol reaction under non-chelating conditions, see Boxer MB, Yamamoto H. J. Am. Chem. Soc 2005;128:48–49. [PubMed: 16390115].
Figure 1.
Two possible transition states for 2,2-dimethyl-3-propanal (22).
Scheme 1.

1 + 2 → SnCl₄

3 → 4

5, 82%

dr = 3.4:1
Scheme 2.
Scheme 3.
Scheme 4.

OTMS

16

TiCl₄, -45 °C, 10 min

1. H₂N₃

H

N₃

n-C₆H₁₃

18

O

n-C₆H₁₃

19, 27%

dr = 32:32:25:11

2. warmed to rt, 24 h

TiCl₄, rt

3 min → -45 °C

OTiClₙ

17

H

N₃

n-C₆H₁₃

-45 °C, 10 min

rt, 24 h

anti-20

19, 56%

major (shown): sum of all minors = 56:44
Scheme 5.

conditions A:
1. TiCl₄ (1 equiv.), allylTMS (1.4 equiv.) CH₂Cl₂, -45 °C, 1 h
2. 3-azidoaldehyde (1.6 equiv.), CH₂Cl₂, -45 °C, 10 min, then 0 °C, 24 h

conditions B:
1. TiCl₄ (1 equiv.), allylTMS (1.4 equiv.) CH₂Cl₂, -45 °C, 1 h
2. 3-azidoaldehyde (1.6 equiv.), CH₂Cl₂, -45 °C, 10 min, then 0 °C, 6 h
3. TiCl₄ (2 equiv.), 0 °C, overnight
Scheme 6.

\[
\begin{align*}
&\text{Ketone 2} + \text{Aldehyde 21} \xrightarrow{\text{TiCl}_4} \text{27} \\
&\text{27} \xrightarrow{\text{TMSCl}} \text{29} \\
&\text{29} \xrightarrow{\text{TiCl}_4} \text{23a} + \text{23b} (38\%, 7.1:1)
\end{align*}
\]
Scheme 7.
Scheme 8.

1. TiCl₄, allylTMS, CH₂Cl₂, -45 °C, 1h
2. 32, CH₂Cl₂, -45 °C, 10 min, then 0 °C, 6 h
3. TiCl₄ (2 equiv.), rt, overnight

1. TiCl₄, allylTMS, CH₂Cl₂, -45 °C, 1h
2. 18/21, CH₂Cl₂, -45 °C, 10 min, then 0 °C, 6 h
3. TiCl₄ (2 equiv.), rt, overnight

R=H  
R=n-C₆H₁₃
Scheme 9.

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Scheme 10.
Scheme 11.
Scheme 12.
Scheme 13.