JOC The Journal of Organic Chemistry

ARTICLE

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Stereoselectivity in Nucleophilic Additions to 3-Azidoalkanals

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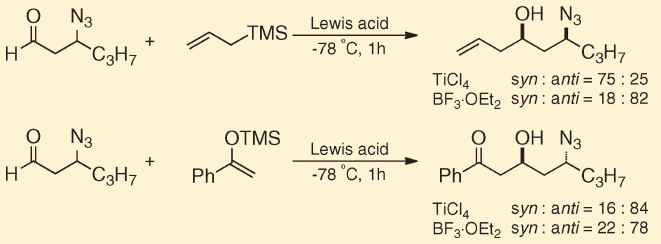
Supporting Information

ABSTRACT: The stereoselectivity of nucleophilic additions to 3-azidoalkanals was investigated. Non-chelating, $BF_3 \cdot OEt_2$-mediated Sakurai addition to 3-azidoalkanals afforded 1,3-*anti* products, whereas use of a chelating Lewis acid, $TiCl_4$, resulted in 1,3-*syn* products with moderate selectivity. A boat-like chelation structure of the 3-azidoalkanal with the Lewis acid is proposed to be consistent with the 1,3-*syn* selectivity of the reactions. Mukaiyama aldol addition to 3-azidohexanal generated 1,3-*anti* products regardless of the chelating ability of the Lewis acid.



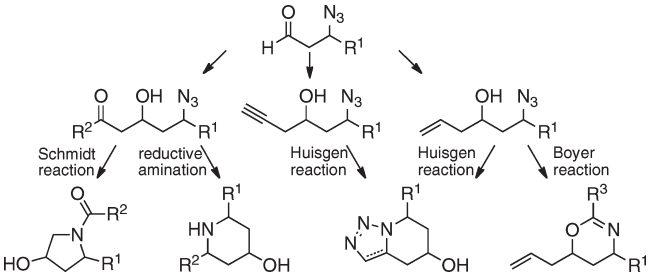
Nucleophilic additions to 3-azidoalkanals, such as the aldol reaction or Sakurai allylation,[1] are useful because the resulting 3-azidoalcohol products can be further functionalized into various heterocyclic compounds such as piperidines via an aza-Wittig cyclization/reduction protocol, pyrazolines via an intramolecular azido-Schmidt reaction,[2] or triazoles via an intramolecular Huisgen reaction[3] (Scheme 1). Work in this laboratory has utilized nucleophilic addition to 3-azidoalkanals as one component of intramolecular azido-Schmidt domino reactions (Scheme 2). For example, we recently reported[4] a domino Sakurai/aldol/Schmidt reaction that involved an aldol addition of an *in situ* generated titanium enolate species to 3-azidononanal. Notably, this reaction resulted in the exclusive formation of a 1,3-*syn* aldol intermediates (**1a** and **1b**). The relative stereochemistry was confirmed by the structures of two final diastereomeric Schmidt products **2a** and **2b**. A second example was a Prins-type nucleophilic addition of alkene **3** to 3-azidononanal, resulting in a mixture of two diastereomeric intermediates **4** favoring *syn* in a 10:1 ratio.[5] Their identities were deduced from the product distribution ratio of recovered starting material **5** and ring-expansion/Schmidt products **6** and **7**. Both were surprising results in that we had not expected a small β-azido group to have a strong effect on the diastereoselectivity of either reaction.

Although nucleophilic additions to 3-azidoalkanals and 3-azidoalkanaldimines have been rarely reported,[6] 1,3-*anti*-stereoselectivity in nucleophilic additions to other 3-heteroatom-substituted aldehydes is well precedented. Reetz's half-chair model[7] and Evans's dipole−dipole interaction model[8] are generally used to explain the observed selectivities in nucleophilic additions to aldehydes under chelation and non-chelation conditions, respectively (Scheme 3). Regardless of whether the reaction stereochemistry is controlled by chelation, the predominant stereochemical outcome in reported nucleophilic additions to 3-heteroatom-substituted aldehydes is 1,3-*anti*.

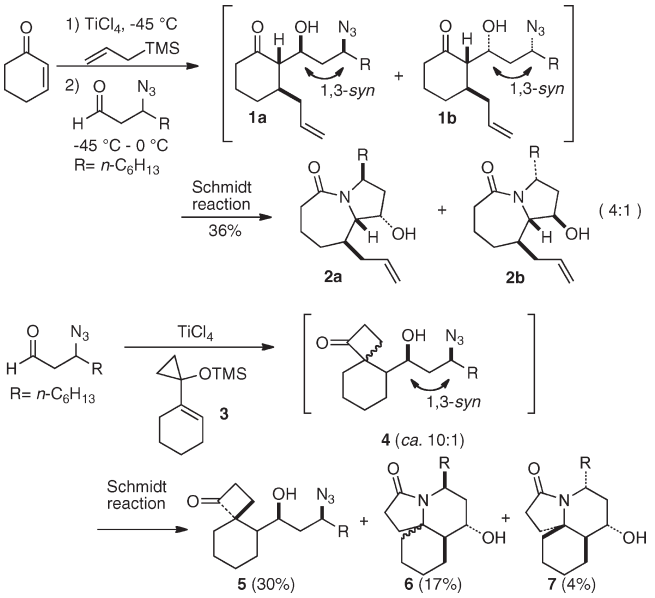
The azido group is electron-withdrawing and has the ability to chelate with metal species.[4,6c,9] Therefore, one would expect that it should behave similarly to an alkoxy group at the 3-position of an aldehyde, which can participate in chelation via Reetz's chelation model or act as an electron-withdrawing group via Evans's non-chelation model, both of which should lead to a 1,3-*anti* product based on the preceding analysis. However, since the above-noted precedents (Scheme 2) suggested 1,3-*syn* selective nucleophilic addition to 3-azidoalkanals under chelation conditions, we decided to further investigate the stereoselectivity of these processes. Accordingly, we surveyed the addition reactions of a variety of nucleophilic species to various 3-azidoalkanals. We began with the Lewis acid mediated allylation under Sakurai conditions as shown in Table 1. The allylation of 3-azidoalkanals with allyltrimethylsilane and mediated by $BF_3 \cdot OEt_2$ have a result in accord with Evans's model and produced *anti*-**8** as the major product (*anti*:*syn* = 82:18) in 41% yield (entry 1). However, the same reaction mediated by $TiCl_4$ resulted in product **8** with low *syn* stereoselectivity (entry 2). To encourage chelation of the carbonyl and azide with the Lewis acid, $TiCl_4$ and 3-azidohexanal were premixed at −78 °C before addition of allyltrimethylsilane (entry 3), which resulted in moderate *syn* stereoselectivity (*syn*:*anti* = 75:25). Change in the size of R^1 did not cause any significant change in stereoselectivity (entries 4 and 5). The similar stereochemical feature was also observed using

Received: January 4, 2011
Published: March 21, 2011

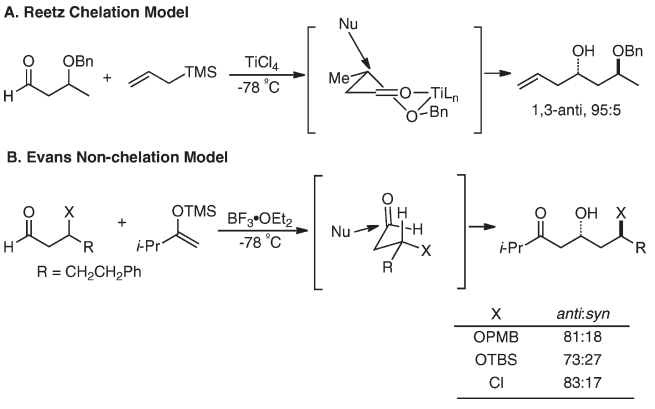
Scheme 1



Scheme 2



Scheme 3



X	*anti*:*syn*
OPMB	81:18
OTBS	73:27
Cl	83:17

trimethylsilylallene[10] as the nucleophile, instead to form homopropargylic alcohol product **10**.

To the best of our knowledge, there is no precedent for the observed 1,3-*syn* selective allylation under chelating conditions.[11] However, both Keck and Evans published models for the *anti* allylation of chelated 1,3-alkoxyaldehydes under conditions analogous to those used here. According to Keck's NMR analysis on the chelate complex of β-alkoxyaldehyde, the size of the alkoxy substituent (benzyl versus methyl) influences the geometry of the chelate structure and thus the stereoselectivity of the reaction (Scheme 4).[12] This observation could not be explained by the traditional Reetz half-chair model shown in Scheme 3. On the basis of his NMR work, Keck proposed that the larger benzyloxy-substituted aldehyde **11** would nudge the adjacent alkyl group into an axial position (**13**), where it would more effectively dictate the high facial selectivity bias of an incoming nucleophile. In contrast, with the smaller methoxy substituent in **14**, the alkyl group on the chelation ring may adopt a pseudoequatorial position (**16**), where the facial selection against incoming nucleophile is less effective.

Later, Evans proposed a boat chelation model of Me_2AlCl/3-alkoxyaldehyde complex for explaining the 1,3-*anti* selectivity based upon PM3-semiempirical calculations (Figure 1).[13] With a larger benzyl group on the oxygen, the 3-alkyl group prefers a pseudoaxial position by 0.9 kcal/mol (**17a** versus **17b**), whereas with the smaller methoxy group shows a preference for a pseudoaxial position by only 0.5 kcal/mol (**18a** versus **18b**). This result is consistent with Keck's observation that stereoselectivity depended on alkoxy group size as noted above. We envisioned that the azido group could be analogous to the alkoxy group where the alkyl group is substituted with a N_2^+ group. Although there is no experimentally determined A value of an N_2^+ group, it should be close to that of a cyano group (0.17) or ethynyl group (0.18) as all three substituents share formal sp hybridization and linear geometries.[14] We propose that the small size of N_2^+ could be responsible for the inversion of stereoselectivity by favoring the placement of a C3-alkyl group in the pseudoequatorial position (**19b**), since there is now no N-alkyl group placed where it could force axial orientation of the C-3 alkyl group.

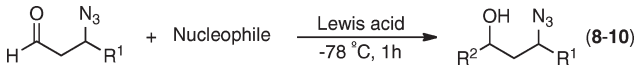
Although our proposed chelated intermediate includes a unique special arrangement leading to the stereochemistry that could not be achieved by traditional substrates, the model implies a limitation on the level of stereoselectivity that can be obtained in this system. The pseudoequatoral C-3 alkyl chain would not effectively block the concave face of the boat structure as does one displayed at the pseudoaxial position. Therefore, increasing the size of C-3 would not affect the stereoselectivity (Table 1, entries 4 and 5). Instead, the stereoselectivity could arise from the interaction between axial $N_2^+$and an incoming nucleophile (either through small steric interaction or cation−cation repulsion).

We next screened various Lewis acids in attempts for improving the unusual 1,3-*syn* selectivity (Table 2). In most cases, no significant *syn* or *anti* selectivity was observed. Only the reaction of allyltributylstannane using $SnCl_4$ promotion provided reasonably high 1,3-*syn* selectivity, which might involve the internal delivery of allyl group from chelated allylchlorostannane structure (Table 2, entry 8).[15]

In contrast to the allylation with allylsilane derivatives, Mukaiyama aldol reactions[16] of 3-azidoalkanal with silyl enol ethers were not generally 1,3-*syn* selective under chelation conditions (Table 3). As expected, the Mukaiyama aldol reaction of 3-azidoalkanals with allyltrimethylsilane mediated by non-chelating Lewis acid $BF_3 \cdot OEt_2$ produced *anti*-**23** and *anti*-**24** as the major product (entry 3 and 5). In entry 4 and 5, additional methyl group on the nucleophile was attached, which resulted in

dx.doi.org/10.1021/jo102597d |*J. Org. Chem.* 2011, 76, 3160–3165

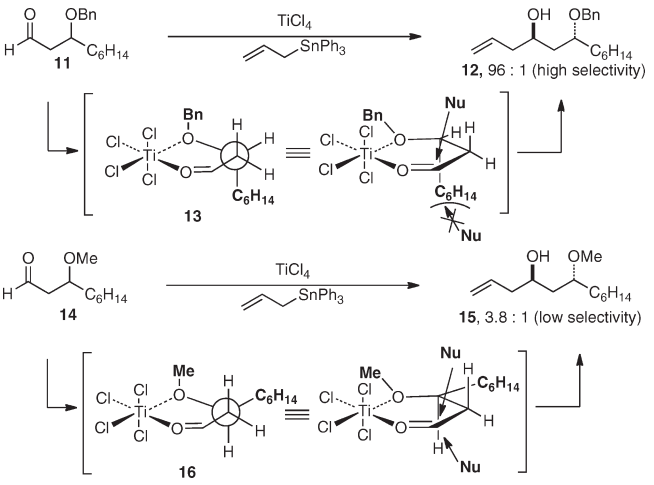
Table 1. Stereoselectivities in Sakurai Additions to 3-Azidoalkanals under Chelation/Non-chelation Conditions



entry	Lewis acid	nucleophile	R^1	R^2	product	yield (%)	*syn*:*anti*[a]
1	$BF_3 \cdot OEt_2$	$H_2C{=}CHCH_2TMS$	*n*-Pr	$H_2C{=}CHCH_2-$	**8**	41	18:82
2	$TiCl_4$	$H_2C{=}CHCH_2TMS$	*n*-Pr	$H_2C{=}CHCH_2-$	**8**	71	62:38
3	$TiCl_4$[b]	$H_2C{=}CHCH_2TMS$	*n*-Pr	$H_2C{=}CHCH_2-$	**8**	73	75:25
4	$BF_3 \cdot OEt_2$	$H_2C{=}CHCH_2TMS$	*i*-Pr	$H_2C{=}CHCH_2-$	**9**	30	12:88
5	$TiCl_4$[b]	$H_2C{=}CHCH_2TMS$	*i*-Pr	$H_2C{=}CHCH_2-$	**9**	75	74:26
6	$BF_3 \cdot OEt_2$	$H_2C{=}C{=}CHTMS$	*n*-Pr	$HC{\equiv}CH_2-$	**10**	22	25:75
7	$TiCl_4$[b]	$H_2C{=}C{=}CHTMS$	*n*-Pr	$HCE{\equiv}CH_2-$	**10**	60	75:25

[a] Determined by ^1H NMR analysis on the crude mixture. [b] Aldehyde was precomplexed with $TiCl_4$.

Scheme 4



generation of all four diastereomers. The ratio between the sum of 1,3-*syn* and 1,3-*anti* product indicates *anti* product is major in both cases (see Supporting Information for determining the stereochemistry). In entries 6 and 7, the bulky silyl enol ether was used to maximize the steric interactions between the nucleophile and the aldehyde-titanium complex, which increased the tendency toward the formation of *syn* diastereomer.

In the Sakurai addition, the allylsilane is generally thought to approach the aldehyde via a *syn-synclinal* transition state[17] (Figure 2A). In this transition state, allylsilane is closer to the N_2^+group, having more steric interaction or cation−cation repulsion between $N_2^+$and the developing partial cationic charge on the allylsilane. In constast, silyl enol ether approach to the aldehyde is in *antiperiplanar* direction[18] (Figure 2B), which would minimize the steric or cation−cation interaction between incoming nucleophile and N_2^+ group. Without any substantial substituent blocking the incoming nucleophile, a concave approach seems to be favored because the bond-forming event from the convex face would result in twisting of the overall chelation structure.

All of the above considerations suggest that the unexpected 1,3-*syn* selectivity in allylation of 3-azidoalkanal with $TiCl_4$ and $SnCl_4$ could originate from the delicate combination of the formation of a boat-like chelation structure and the nature of the Lewis acid/nucleophile. The ability to obtain *syn* adducts with suitable choices of nucleophile and Lewis acid, even in modest diastereoselectivities, from 3-azidoalkanals stands in contrast to the reported behavior of other 3-heteroatom-substituted aldehydes.

Manipulation of Adducts. Selected addition products of the 1,3-azido aldehydes were subjected to further chemical modification in order to both (1) provide cyclic structures that would permit the unambiguous determination of product diastereoselectivity and (2) exemplify the sorts of downstream products that can be accessed through these reactions (Scheme 5). Therefore, azidoalkyne **10** was transformed into triazole **26** by an intramolecular [3 + 2]-cycloaddition. The relative configuration of azidoketone **23** was determined by forming the piperidine **27** using an aza-Wittig reaction followed by reduction.

Other kinds of azido-Schmidt reactions developed by our group also lead to attractive product types (Scheme 6). Therefore, reaction of **9** with benzaldehyde under Lewis acid conditions provided the cyclic benzimidate **28** in 44% yield.[19] NOE analysis was used to determine the stereochemistry of **9**. In addition, an intramolecular azido-Schmidt reaction was also used for constructing a cyclic amide. Thus, a $TiCl_4$-mediated Schmidt reaction of **24a** afforded both an alkyl-migrated Schmidt product **29** and a presumably phenyl-migrated product **30** (combined yield 72%, 63:37). The relative stereochemistry of **29** was determined after reducing the amide with $LiAlH_4$ and NOESY analysis of the resulting pyrrolidine (see Supporting Information).

Summary. The stereoselectivity of nucleophilic addition reactions of β-azido aldehydes has been examined in several contexts. When reacted with allylating reagents under conditions consistent with internal chelation, *syn* products were obtained as major isomers in contrast to results previously published efforts of other β-heteroatom-containing substrates, which afford *anti* products under similar conditions. When Mukaiyama aldol conditions were used instead, regardless of whether chelating or non-chelating conditions were employed, *anti* 1,3-azidoalcohols were obtained as major products. The utility of these reaction has been briefly demonstrated by examining several downstream reactions of the resulting 1,3-azidoalcohols.

EXPERIMENTAL SECTION

Representative Sakurai Reaction Procedure Mediated by $TiCl_4$: 6-Azidonon-1-en-4-ol (8). To a stirred solution of

dx.doi.org/10.1021/jo102597d |J. Org. Chem. 2011, 76, 3160–3165

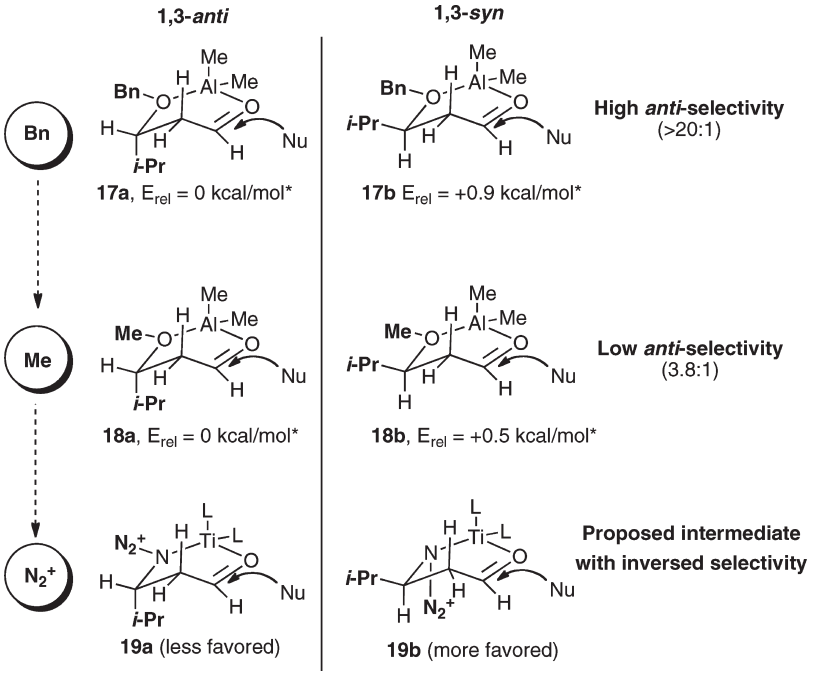
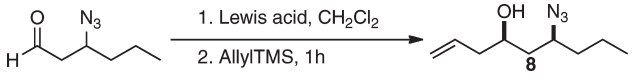


Figure 1. Proposed structure of the boat-like Lewis acid chelation with 3-alkoxyaldehyde and 3-azidoalkanal.

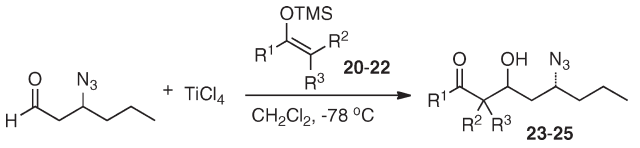
Table 2. Stereoselectivities in Sakurai Addition to 3-Azidoalkanal with Various Chelating Lewis Acids



entry	Lewis acid	yield (%)	*syn*:*anti*[a]	comments
1	$TiCl_4$	73	75:25	completed in 10 min
2	TiF_4	0	undetermined	
3	$Ti(O/\text{-}Pr)Cl_3$	19	31:69[b]	
4	Me_2AlCl	37	17:83	
5	$AlCl_3$	<5	undetermined	insoluble in CH_2Cl_2
6	$Sc(OTf)_3$	19	24:76[b]	insoluble in CH_2Cl_2
7	$SnCl_4$	55	54:46	
8	$SnCl_4$	75	76:24[c]	

[a] Determined by ^{1}H NMR analysis on crude mixture. [b] Determined after purification (complicated crude ^{1}H NMR spectrum). [c] Nucleophile was allyltrichlorostannane generated in situ by transmetalation of allyltributylstannane.

Table 3. Stereoselectivities in Mukaiyama Aldol Reaction with 3-Azidoalkanal under Chelating/Non-chelating Conditions



entry	silyl enol ether	R^1	R^2	R^3	Lewis acid	product	yield (%)	*syn*:*anti*[a]
1	**20**	Ph	H	H	$TiCl_4$	**23**	74	16:84
2	**20**	Ph	H	H	Me_2AlCl	**23**	54	31:69
3	**20**	Ph	H	H	$BF_3\cdot OEt_2$	**23**	66	22:78
4	**21**	Ph	Me	H	$TiCl_4$	**24**	31	33:67[b]
5	**21**	Ph	Me	H	$BF_3\cdot OEt_2$	**24**	64	18:82[b]
6	**22**	Ph	Me	Me	$TiCl_4$	**25**	78	47:53[c]
7	**22**	Ph	Me	Me	Me_2AlCl	**25**	25	66:36

[a] Determined by ^{1}H NMR analysis on crude mixture. [b] Reaction generated 4 diastereomers. Ratio between sum of 1,3-*syn* and sum of 1,3-*anti* products and detail in Supporting Information. [c] Determined after purification (complicated crude ^{1}H NMR spectrum).

3-azidohexanal (150 mg, 1 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added $TiCl_4$ (0.13 mL, 1.2 mmol) dropwise via syringe. The resulting yellow solution was added allyltrimethylsilane (0.24 mL, 1.5 mmol) dropwise after 5 min. TLC analysis indicated that the reaction was complete within 5 min. Reaction was quenched with aqueous saturated $NaHCO_3$ solution (10 mL), warmed to rt, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was purified by column chromatography (SiO_2, 20% EtOAc/hexanes) to afford known product **8**[6b] as a mixture of two diastereomers in 71% yield. The diastereomeric ratio between *syn*-**8** and *anti*-**8** was 75:25 according to the crude NMR analysis (see Figure 3). (4*R**,6*S**)-6-Azidonon-1-en-4-ol (*syn*-**8**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.32−1.59 (m, 5H), 1.61- 1.67 (m, 1H), 2.13−2.32 (m, 2H), 2.45 (br s, 1H), 3.44−3.51 (m, 1H), 3.76−3.82 (m, 1H), 5.08−5.12 (m, 1H), 5.12−5.15 (m, 1H), 5.74−5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.1, 36.4, 40.7, 41.9, 60.4, 68.7, 118.3, 134.2. IR (neat) 3400 (br), 2960, 2935, 2098 cm^{-1}. (4*R**,6*R**)-6-Azidonon-1-en-4-ol (*anti*-**8**): ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 3.57−3.62 (m, 1H), 3.83−3.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.3, 37.1, 41.3, 42.5, 59.5, 67.3, 118.3, 134.3.

Representative Sakurai Reaction Procedure Mediated by $BF_3\cdot OEt_2$. To a stirred solution of 3-azidohexanal (150 mg, 1 mmol) and allytrimethylsilane (0.24 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) at −

dx.doi.org/10.1021/jo102597d |*J. Org. Chem.* 2011, 76, 3160–3165

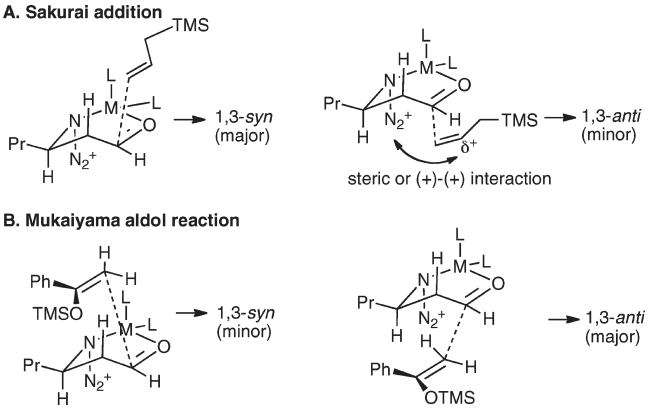


Figure 2. Transition state comparison between Sakurai addition and Mukaiyama aldol reaction.

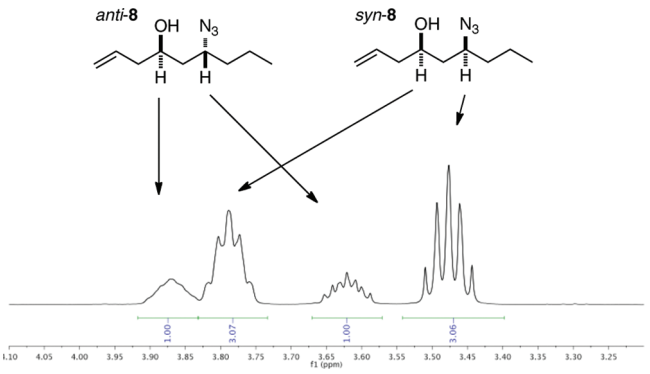
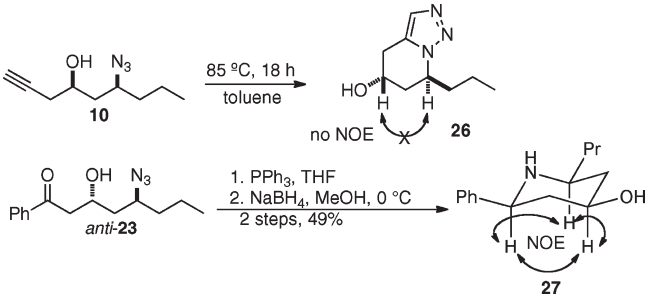


Figure 3. Determination of diastereomeric ratio by crude ^{1}H NMR analysis.

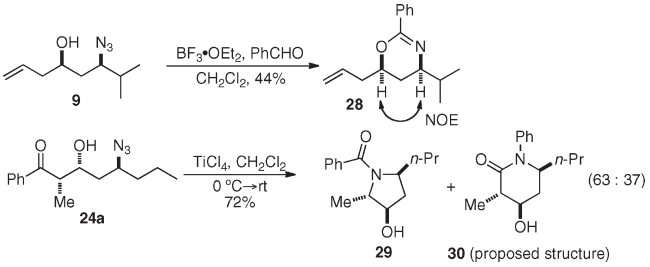
Scheme 5



78 °C was added $BF_3 \cdot OEt_2$ (0.15 mL, 1.2 mmol) dropwise via syringe. After 1 h at −78 °C, the same workup and purification procedure was followed as before to afforded **8** in 41% (*syn*:*anti* = 18:82)

Representative Mukaiyama Aldol Reaction by $TiCl_4$: Azido-3-hydroxy-1-phenyloctan-1-one (23). Freshly prepared 3-azidohexanal (0.142 g, 1.01 mmol) and silyl enol ether **20** (0.211 g, 1.10 mmol) were dissolved in 24 mL of CH_2Cl_2. The mixture was cooled to −78 °C, and 1.1 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added dropwise. The reaction mixture was stirred at −78 °C for 1 h. The flask was removed from the cold bath and immediately quenched with the slow addition of saturated, aqueous NH_4Cl (24 mL). When stirring became impeded by frozen ice, quenching was stalled until the mixture resumed adequate consistency. The biphasic mixture was separated, and

Scheme 6



the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a crude oil. A sample of the crude oil was analyzed by HPLC (ratio of *syn*-**23**:*anti*-**23** = 23:77, for detail, see Supporting Information). The crude product was purified by column chromatography on silica gel (5% EtOAc in hexanes) to afford the product as a clear, colorless oil (52% yield, mixture of diastereomers). A pure sample of diastereomer *anti*-**23** was obtained by column chromatography (CH_2Cl_2). Major diastereomer (*anti*-**23**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3H), 1.39−1.67 (m, 5H), 1.75 (ddd, J = 13.9, 10.4, 2.8 Hz. 1H), 3.09 (dd, J = 17.8, 8.8 Hz, 1H), 3.20 (dd, J = 18.0, 2.8 Hz, 1H), 3.53 (dd, J = 3.6, 1.6 Hz, 1H), 3.70−3.79 (m, 1H), 4.47 (m, 1H), 7.46−7.51 (m, 2H), 7.62 (t, 1H), 7.94−7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.4, 37.3, 41.3, 45.2, 59.3, 64.7, 128.1, 128.8, 133.7, 136.6, 200.5; IR (CH_2Cl_2) 3400, 2100, 1680 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_3O_2$ 262.1555, found 262.1564. Minor diastereomer (*syn*-**23**, diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84−1.93 (m, 1H), 3.49 (m, J = 2.8 Hz, 1H), 3.61 (m, 1H), 4.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 36.2, 40.5, 44.9, 59.7, 65.5, 200.3.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and stereochemical assignment for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the National Institute of General Medical Sciences (GM 049093 and GM 069663) for financial support.

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