Trifluoroacetic Acid Salt of (±)-*cis*-5-Methylprolinamide (25). A solution of the trifluoroacetic acid salt **24a** (0.040 g, 0.16 mmol) in 4% methanolic ammonia (2 mL) was left at room temperature for 5 days. The solvent was removed in vacuo, trifluoroacetic acid was added to the residue, and after evaporation in vacuo the residue was purified by column chromatography on Sephadex LH-20 (1.4 × 40 cm) with methanol as the eluant. The product (0.035 g, 93%) on crystallization from ethyl acetate–hexane had mp 124 °C. The NMR spectrum and TLC [ethyl acetate–triethylamine (96:4)] were identical with L-*cis*-5-methylprolinamide trifluoroacetic acid salt:[14] exact mass (high-resolution mass spectrum) calcd for $C_6H_{12}N_2O$ 128.0950, found 128.0949.

***cis*-1-Benzyl-2,5-dimethylpyrrolidine (29).** A solution of the mixture of **27** and **28** (0.500 g, 2.5 mmol) in 2 N methanolic hydrochloric acid (10 mL) was heated at reflux temperature for 2.5 h. The solution was evaporated to dryness in vacuo and the crystalline solid which remained was washed with ethyl acetate. The solid thus obtained (0.34 g) was dissolved in acetone (10 mL) containing benzyl bromide (0.50 g, 2.9 mmol) and suspended sodium carbonate (0.50 g), and the mixture was heated at reflux temperature for 2 h. The solvent was evaporated in vacuo, the residue was triturated with ether, the mixture was filtered, and the filtrate was evaporated in vacuo. Methanolic hydrogen chloride was added to the residue, the solution was evaporated in vacuo and the residue was twice crystallized from ethyl acetate. The hydrochloride salt thus obtained was decomposed with saturated sodium carbonate solution and the free base was extracted into ether. The solvent was removed in vacuo and the residual oil was distilled in vacuo to give pure **29** (0.161 g, 34%): bp 60 °C (0.1 mm). The NMR spectrum of this material was identical with the published spectrum of *cis*-1-benzyl-2,5-dimethylpyrrolidine.[16]

Acknowledgment. The authors gratefully acknowledge the extra effort on our behalf by D. Cho, Analytical Research, in measuring the high-resolution mass spectra.

Registry No. **4a**, 92012-07-2; **4b**, 92012-08-3; **5a**, 92012-09-4; **5b**, 92012-10-7; **6b**, 92012-11-8; **7a**, 92012-12-9; **7b**, 92012-13-0; **8a**, 92012-14-1; **8b**, 92012-15-2; **9a**, 92012-16-3; **9b**, 92012-17-4; **10a**, 92012-18-5; **10b**, 92012-19-6; **11a**, 92012-20-9; **11a** (*N*-debenzyl deriv), 92012-21-0; **12**, 75400-61-2; **13**, 92012-22-1; **14**, 33234-48-9; **15a**, 92012-23-2; **15b**, 92012-24-3; **16a**, 92012-25-4; **16b**, 92012-26-5; **17a**, 92012-27-6; **17b**, 92012-28-7; **18**, 92012-29-8; **19**, 92012-31-2; **20a**, 92012-32-3; **20a**·HCl, 92077-34-4; **20b**, 92012-33-4; **20b**·HCl, 92077-35-5; **21a**, 1194-97-4; **21b**, 92012-34-5; **22a**, 92012-35-6; **22b**, 92012-36-7; DL-**23a**, 92012-37-8; DL-**23b**, 92012-38-9; DL-**24a** (X = CF_3CO_2), 92012-44-7; DL-**24b** (X = CF_3CO_2), 92012-40-3; DL-**24b** (X = Cl), 92012-41-4; (±)-**25**·CF_3CO_2H, 92077-37-7; **26**, 50585-36-9; **27**, 92012-42-5; **28**, 92012-43-6; **29**, 4209-68-1; **29**·HCl, 4209-69-2; PhCOCl, 98-88-4; C_2H_5OCOCl, 541-41-3; NH_3, 7664-41-7; $PhCH_2Br$, 100-39-0; Rh, 7440-16-6; Pt, 7440-06-4; PtO_2, 1314-15-4; 2-benzoylpyrrole, 7697-46-3; [4-(benzyloxy)benzoyl]morpholide, 92012-45-8; 4-(benzyloxy)benzoic acid, 1486-51-7; morpholine, 110-91-8; 2-[4-(benzyloxy)benzoyl]pyrrole, 92012-46-9; pyrrole, 109-97-7; di-*tert*-butyl dicarbonate, 24424-99-5; [4-(methoxy)-benzoyl]morpholide, 7504-58-7; 2-acetylpyrrole, 1072-83-9; 2,5-dimethylpyrrole, 625-84-3.

Supplementary Material Available: Table III, giving the IR and NMR spectral data of the pyrrolidine derivatives, and Table IV, giving the C, H, and N analytical figures for the compounds listed in Table II (4 pages). Ordering information is given on any current masthead page.

Stereoconservative Reductive Methyl- and Dimethylamination of Isomeric 3,3-Diarylpropenals. Synthetic and Mechanistic Studies on Control of the Stereochemistry

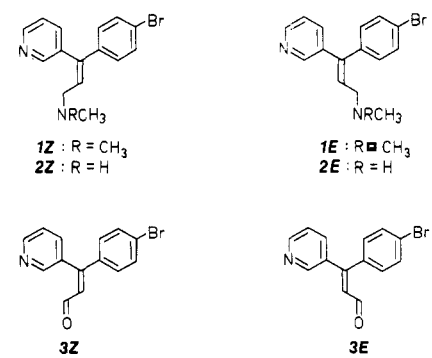
Thomas Högberg* and Bengt Ulff

Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden

Received February 17, 1984

The tertiary allylic amine zimeldine (**1Z**) and the secondary amine **2Z** have been prepared by reductive aminations of (*Z*)-3-(4-bromophenyl)-3-(3-pyridyl)propenal (**3Z**) with sodium cyanoborohydride in the presence of dimethylammonium and methylammonium chloride. The reductive methylamination was largely stereoconservative, giving >96% of the *Z* isomer **2Z**, over a very large pH interval. However, the degree of isomerization in the reductive dimethylamination of **3Z** increased with higher pH. The isomerization showed a first-order dependence on free dimethylamine, inferring a Michael-induced isomerization of the intermediate iminium ion **8** by attack of amine. The rate of isomerization was identical for the two isomeric aldehydes **3Z** and **3E**. The reductive amination of both **3Z** and **3E** was completely stereoconservative (>99%) at low pH with both $MeNH_2$ and Me_2NH.

The antidepressant zimeldine[1] (**1Z**) and its primary metabolite norzimeldine (**2Z**) have been synthesized by several methods including dehydration,[2a] Wittig reaction,[2a] stereoselective allylic rearrangements,[2b,c] and palladium-catalyzed amination.[2d] The difference in biological effects of the *Z* isomers **1Z** and **2Z** and the *E* isomers **1E** and **2E** emphasizes the importance of controlling the stereochemistry of the double bond.[2c] In connection with metabolic studies we required a way of introducing various amine substituents in a stereospecific manner. The reaction should be applicable also for derivatives having the pyr-

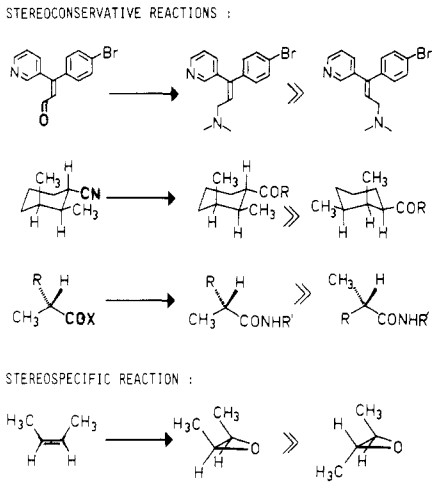


(1) Revised rINN name. Earlier zimelidine.

(2) (a) Carnmalm, B.; de Paulis, T.; Högberg, T.; Johansson, L.; Persson, M.-L.; Thorberg, S.-O.; Ulff, B. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 91–99. (b) Högberg, K.; Lindgren, J.-E.; Högberg, T.; Ulff, B. *Acta Pharm. Suec.* **1979**, *16*, 299–308. (c) Högberg, T.; Ulff, B.; Renyi, A. L.; Ross, S. B. *J. Med. Chem.* **1981**, *24*, 1499–1507. (d) Bäckvall, J.-E.; Nordberg, R. E.; Nyström, J.-E.; Högberg, T.; Ulff, B. *J. Org. Chem.* **1981**, *46*, 3479–3483.

0022-3263/84/1949-4209$01.50/0

Scheme I



idine nitrogen oxidized, since both oxidation levels are indicated from the metabolites isolated.[3]

Reductive amination of carbonyl compounds with sodium cyanoborohydride is a widely used way of making amines.[4] However, with conjugated aldehydes this reaction has been rather scantily investigated.[4b,5] The reaction has been accompanied by double bond reduction[5a] and formation of 1,3-diamino derivatives[5b] via Michael addition of hydride and amine, respectively. In our case it was desirable to transform an aldehyde like **3Z** to **1Z** or **2Z** with stereoconservation,[6] i.e., with retention of the *Z* configuration. These preliminary studies have been communicated,[7] and some tentative metabolites of zimeldine (**1Z**) have been prepared by reductive dimethylamination and *N*-methylhydroxylamination of **3Z** and its *N*-oxide.[8]

In preliminary studies of reacting **3Z**, dimethylamine and $NaBH_3CN$ under standard conditions[4a] in methanol at pH ~7, we observed variations between the experiments in the relative amounts of isomeric amines **1Z** and **1E** formed. Furthermore, this isomerization showed an unexpected pH dependence.[7] To our knowledge, other studies on the stereochemical outcome of reductive amination of unsymmetrically substituted α,β-unsaturated carbonyl compounds are lacking. These facts prompted us to study the reaction in further detail in order to establish the factors controlling the isomerization. The aldehydes **3Z** and **3E** are suitable models, since none of the isomeric products **1Z** and **1E** or **2Z** and **2E** (eq 1) are formed with thermodynamic preference (vide infra).

$$\mathbf{3Z} \rightarrow \mathbf{1Z,2Z} + \mathbf{1E,2E} \leftarrow \mathbf{3E} \qquad (1)$$

Scheme II

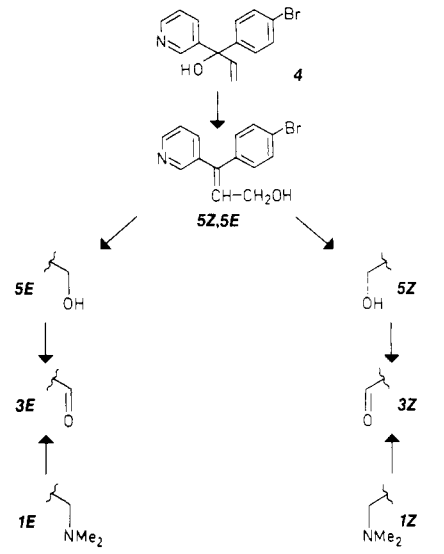


Table I. Reductive Amination of Aldehyde 3Z or 3E (1 equiv) with $RMeNH_2^+Cl^-$ (10 equiv) and $NaBH_3CN$ (1.5 equiv) at Different pH in Methanol[a]

						amine 1 or 2	
entry	3	R	NaOH, equiv	HCl, equiv	approx pH[b]	isolated yield **E** + **Z**	**Z**,[c] %
1	**Z**	Me		0.5	2.3	20	99
2	**Z**	Me		0.2	3.0	85	99
3	**Z**	Me			5.5	85[d]	99
4	**Z**	Me	0.5		8.1	86	95
5	**Z**	Me	1		8.3	75	86
6	**Z**	Me	4		8.9	70	79
7	**Z**	Me	8		9.6	68	70
8	**E**	Me			5.6	95[d]	1
9	**Z**	H			4.4	56[e]	99
10	**Z**	H	0.5		6.8	51	98
11	**Z**	H	1		8.6	51	98
12	**Z**	H	2		9.0	54	97
13	**Z**	H	4		9.6	43	96
14	**Z**	H	8		11.7	27	96
15	**E**	H			4.5	52[e]	1

[a] The reaction was run in methanol at room temperature overnight (20 h) in the presence of molecular sieves (Experimental Section). [b] The pH was measured after addition of aldehyde **3**, $RMeNH_2^+Cl^-$, and NaOH (*x* equiv) or HCl (*y* equiv) in methanol. [c] Analyzed by capillary GLC equipped with an electronic integrator. [d] Reaction time 30 min. No molecular sieves. [e] Reaction time 4 h. No molecular sieves.

Results and Discussion

The required isomeric aldehydes **3Z** and **3E** were made in two ways as outlined in Scheme II. The tertiary allylic alcohol **4** was rearranged with aqueous sulfuric acid to a 60:40 mixture of **5Z,5E**. The *Z* isomer **5Z** was isolated by fractional crystallizations and the *E* isomer **5E** was precipitated as picrate from the mother liquors. Pure **5Z** and **5E** were obtained in 33% and 24% overall yield from **4**, respectively. The stereostructure was established by UV and ^1H NMR as described earlier.[2,3] Oxidation with manganese dioxide in chloroform gave the corresponding aldehydes **3Z** and **3E**. Alternatively, the tertiary amines **1Z** or **1E**, available from large scale production, could be directly oxidized with MnO_2 in refluxing $CHCl_3$ according to the biomimetic procedure previously described for **3Z**.[3] These oxidations were all completely stereoconservative.

The stereostructure of conjugated compounds of this type (e.g., aldehydes **3**) cannot be unambigously assigned by UV and ^1H NMR in contrast to many allylic derivatives such as **1**, **2**, and **5**.[2,3] However, lanthanide-induced shifts

(3) Lundström, J.; Högberg, T.; Gosztonyi, T.; de Paulis, T. *Arzneim.-Forsch.* **1981**, *31*, 486–494.

(4) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904. (b) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201–246. (c) Lane, C. F. *Synthesis* **1975**, 135–146.

(5) (a) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332–4334. (b) Andrews, M. G.; Mosbo, J. A. *J. Org. Chem.* **1977**, *42*, 650–652.

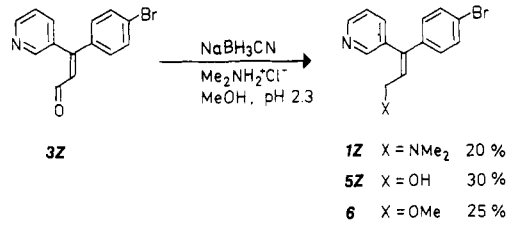
(6) The terms *stereoconservation* and *stereoconservative reaction* have been proposed to be used when a functional group transformation takes place without affecting the stereochemistry in another part of the molecule.[7] Such transformations are often referred to as stereospecific reactions, but we feel this is not as originally intended,[9] since the structural unit with defined stereochemistry is not a reaction center (cf. Scheme I).

(7) Högberg, T.; Lundström, J.; Ulff, B. North American Medicinal Chemistry Symposium, Toronto, Canada, June, 1982; Abstr. p 89.

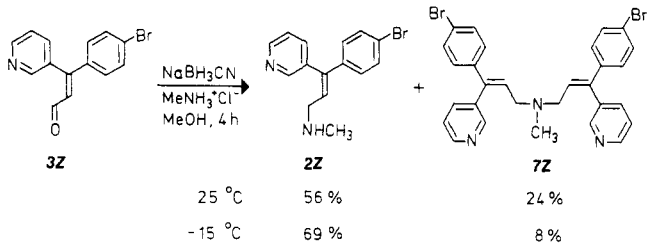
(8) Högberg, T.; Lundström, J. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 85–89.

(9) (a) Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108–116. (b) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 434–446.

Scheme III



Scheme IV



(LIS) in ^{1}H NMR have been utilized in related cases (conjugated nitriles)[2a] as well as for various tertiary amines.[10,2c,d] The lanthanide reagent [Eu(fod)$_3$] coordinates to the pyridine nitrogen and the Z/E configuration of the two aldehydes **3** follows from comparisons of LIS of the vinyl proton with the 2-pyridyl or aldehyde proton. Thus, the LIS gradient (slope of shift diagrams) ratios G(vinyl)/G(2-pyridyl) is 0.28 for **3E** and 0.19 for **3Z** and G(vinyl)/G(aldehyde) is 2.0 for **3E** and 0.55 for **3Z**.[11] These data confirm the cis relationship of the vinyl proton and the pyridine ring in **3E**.

Synthetic Studies. Arbitrarily, aldehyde **3** was mixed with a large excess of either $Me_2NH_2^+Cl^-$ or $MeNH_3^+Cl^-$, having the pH adjusted by addition of NaOH or HCl, and was finally treated with $NaBH_3CN$ in methanol. The first series of experiments, run overnight in the presence of molecular sieves, are outlined in Table I. There is a striking difference in the reductive dimethylamination (entries 1–7) and the methylamination (entries 9–14) of aldehyde **3Z**. The latter reaction was largely stereoconservative, giving 96% or more of Z isomer **2Z**, over a very large pH interval. On the other hand, reaction with Me_2NH resulted in a pronounced isomerization during standard conditions[4a] (entry 6). However, when pH is reduced the reaction is stereoconservative and proceeds in high yield (entries 2 and 3). Furthermore, the reaction is surprisingly fast. A complete conversion was observed by gas chromatography within 10 min with no addition of NaOH (entry 3). The presence of molecular sieves also proved to be superfluous (entries 3, 8, 9, and 15). The aldehyde **3E** was also aminated in good yield with complete stereoconservation to give **1E** and **2E** under the same conditions (entries 8 and 15).

When pH is lowered too much (entry 1) the reaction is much slower and several other reactions are competing as shown in Scheme III. The formation of alcohol **5Z** is expected at such a low pH.[4] The methyl ether **6**, formed via the acetal or hemiacetal,[12] is also precedented from reduction of α,β-unsaturated carbonyl compounds with $NaBH_3CN$ in methanol.[13]

(10) Högberg, T. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 629–632.
(11) A thorough discussion of this calculation technique for LIS of related allylic amines can be found in ref 10. See also Experimental Section.
(12) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, *16*, 1357–1358.
(13) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530–2533.

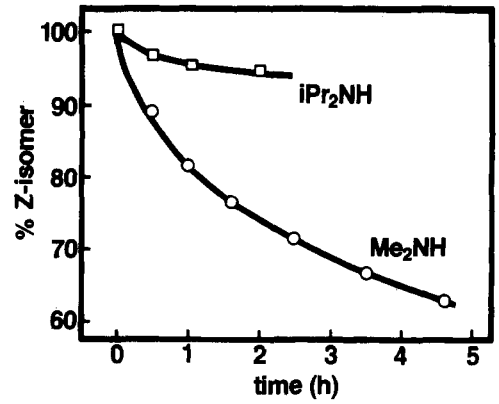
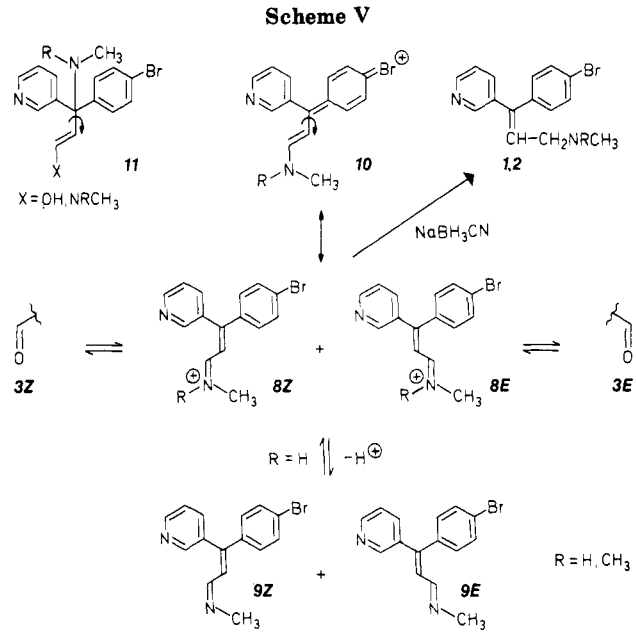


Figure 1. Isomerization of Z aldehyde **3Z** (0.07 M) in methanol with addition of 0.5 equiv of dimethylamine or diisopropylamine at room temperature.

Scheme V



The reactions with methylamine suffered from extensive dialkylation even with a 10:1 ratio of amine to aldehyde. As can be seen in Scheme IV the dialkylation can be effectively suppressed by lowering the reaction temperature to ca. −15 °C. The dialkylated product **7Z** can be separated from **2Z** by extraction with ether at pH ~5 (entry 9). This product (**7Z**) was identical (^{1}H NMR, MS) with **7Z** obtained as byproduct from reaction of $MeNH_2$ with the corresponding Z allylic chloride (cf. ref 2b). The ^{1}H NMR and especially UV (λ_{max} 251 nm) confirmed the Z configuration of **7Z**. Similarly, the corresponding dialkylated E isomer **7E** was isolated as byproduct from reductive methylamination of **3E** (entry 15) in 22% yield (λ_{max} 220 nm).

Mechanistic Studies. There are two principle ways of isomerization in this reaction: rotation of a single bond in a resonance form, preferably **10**, or in a Michael adduct of type **11** (Scheme V). The resonance-mediated isomerization of the iminium ion **8** via **10** is less likely, especially in the case of **3Z**, since the 4-bromophenyl ring can be coplanar with the olefinic part in **8Z** but not easily in **8E** due to steric hindrance. This fact would favor the Z form if isomerization occurred by this mechanism (see discussion in connection with Figure 2 (x = 0) below).

Michael-induced isomerization via **11** can take place at several points: aldehyde **3**, iminium ion **8**, or in the methylamine case, imine **9**. The reductive dimethylamination is clearly most sensitive to isomerization (Table I) and

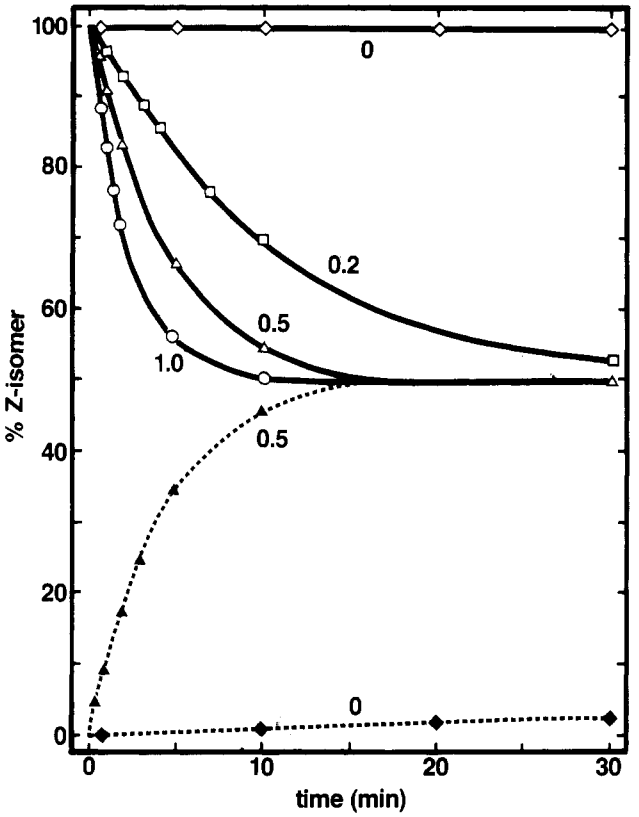


Figure 2. Percentage of *Z* isomer of allylamine 1 obtained after treatment of aldehyde **3Z** (solid lines) or **3E** (dashed lines) with $Me_2NH_2^+Cl^-$ (10 equiv) and NaOH (x equiv) for t min followed by quenching with $NaBH_3CN$ (see Experimental Section): ◇◆, x = 0; □, x = 0.2; △▲, x = 0.5; ○, x = 1.0.

accordingly we investigated the first Michael mode with this amine (Me_2NH) in comparison with a bulkier secondary amine (i-Pr_2NH). The isomerization of aldehyde **3Z** in methanol induced by the two amines in base form were followed by gas chromatography (Figure 1). Dimethylamine caused a more rapid isomerization than the sterically hindered diisopropylamine. However, the rate of isomerization is far too slow to explain the isomerization in connection with the reductive amination. This indicates that a more reactive acceptor than the conjugated aldehyde is required for the Michael mode of isomerization. Furthermore, it would not explain the difference in isomerization between reductive methylamination and dimethylamination (Table I).

The iminium ion **8**, which is a more reactive Michael acceptor than the uncharged **3** and **9**, cannot relieve its charge when R = Me. However, in the case of R = H the equilibrium is shifted to the deprotonated imine **9** at higher pH, due to the higher basicity of methylamine present (Scheme V). Isomerization caused by attack on **8** is in line with the different behavior of Me_2NH and $MeNH_2$ as well as with the observed increased degree of isomerization in the former case when a larger fraction of free Me_2NH is present at higher pH (Table I, entries 3–7).

In order to verify this mechanism we took advantage of the rapid reduction (especially with Me_2NH) in the following quenching experiments. Aldehyde **3** (1 equiv) was treated with $RMeNH_2^+Cl^-$ (10 equiv) and NaOH (x equiv) in methanol. Aliquots were withdrawn at various times and reacted with $NaBH_3CN$. The Z/E ratio of secondary amines **2** (Table II) or tertiary amines **1** (Figure 2) formed was analyzed by gas chromatography. When R = H the isomerization is slow even when an excess of $MeNH_2$ in base form is present (x = 2), which is consistent with the

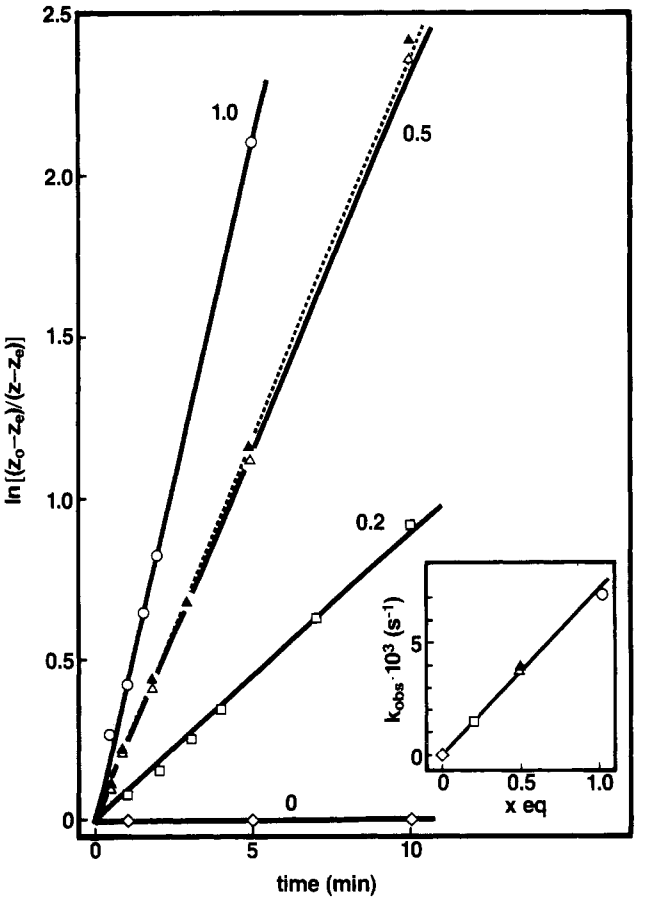


Figure 3. Pseudo-first-order kinetic plots of isomerization experiments with aldehyde **3Z** or **3E** (1 equiv), $Me_2NH_2^+Cl^-$ (10 equiv), and NaOH (x equiv) shown in Figure 2. z = % **1Z** formed after quenching with $NaBH_3CN$ at t min; z_e = 50% at equilibrium; z_0 at t = 0. Insertion shows dependence of the observed rate constant on the number of equivalents (x) of NaOH ≈ free $HNMe_2$: ◇, x = 0; □, x = 0.2; △▲, x = 0.5; ○, x = 1.0.

Table II. Percentage of *Z* Isomer of Allylamine 2 Obtained after Treatment of *Z* Aldehyde 3Z (1 equiv) with $MeNH_3^+Cl^-$ (10 equiv) and NaOH (x equiv) for t Min Followed by Quenching with $NaBH_3CN$[a]

time, min	equiv of NaOH		
	x = 0	x = 0.5	x = 2.0
1.0	100	100	94
10	100	99	92
30	99	97	89

[a] See Experimental Section.

fact that reductive methylamination is essentially stereoconservative over a large pH interval (Tables I and II).

This is in strong contrast to the analogous experiment with Me_2NH and **3Z** or **3E** shown in Figure 2. In the case of **3Z**, the isomerization is negligible when no Me_2NH in base form is present (x = 0) but with **3E** a very slow albeit significant isomerization takes place. These findings might indicate operation of a resonance-mediated isomerization from **3E** via **10** (Scheme V), although this mechanism cannot play a significant role under normal conditions for reductive amination shown in Table I. However, a rapid isomerization takes place even with small amounts of free Me_2NH (Figure 2). An equilibrium mixture containing the amine isomers **1Z** and **1E** in a 50:50 ratio was formed from either aldehyde **3Z** or **3E**.

The isomerization observed (measured as 1) follows pseudo-first-order kinetics over the investigated 5-fold range of added amount of NaOH (Figure 3). The rate of

isomerization is identical for the two isomeric aldehydes (at $x = 0.5$). Furthermore, the observed rate constants are linear in the number of equivalents (x) of NaOH added, inferring first-order dependence on free dimethylamine (see insertion Figure 3). These facts make isomerization via Michael attack on 8 with $HNMe_2$ very likely. This also explains the problems in reproducing the reductive dimethylaminations at higher pH (Table I, entries 4–7), since even small differences in time delay in the addition of $NaBH_3CN$ will have a large effect on the Z/E ratio of 1.

Conclusions

The studies on the isomerization observed during reductive amination with *dimethylamine* can be summarized as follows: Firstly, the resonance-mediated isomerization mode is not competitive in this case with such a modest electron donor as bromine. Secondly, the Michael-induced isomerization requires a more reactive acceptor than the conjugated aldehyde **3**, i.e., the charged iminium ion **8**. Thirdly, the isomerization rate of **8** is directly proportional to the concentration of nucleophile (Me_2NH in base form) available for Michael attack. Finally, this mode of isomerization also rationalizes the low degree of isomerization observed for the corresponding reaction with *methylamine*, since high concentrations of nucleophile ($MeNH_2$ in base form) and charged Michael acceptor **8** cannot be present simultaneously. However, the reductive amination is completely stereoconservative at low pH with both secondary (Me_2NH) and primary ($MeNH_2$) amine.

Experimental Section

Melting points were determined on a Mettler FP 61 apparatus in open capillary tubes and are uncorrected. ^1H NMR spectra in $CDCl_3$ were recorded on a Varian T-60 spectrometer and the chemical shifts are reported in δ (ppm) units relative to internal Me_4Si. UV spectra in 0.1 M HCl were obtained on a Zeiss DMR 21. Mass spectra (EI, 70 eV) were recorded on an LKB 9000. GLC were run on an OV 1 or SE 30 capillary column and the amounts determined by a Hewlett-Packard 3390A integrator assuming identical response factors (detection limit ca. 1% of minor isomer). TLC were run on SiO_2 according to ref 3. Elemental analyses, performed by Analytische Laboratorien, Elbach, West Germany, were within ±0.4% of the theoretical values.

3-(4-Bromophenyl)-3-(3-pyridyl)-2-propen-1-ol (5Z and 5E). 1-(4-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol[2d] (**4**, 58.0 g, 200 mmol) was rearranged in 500 mL of 1 M H_2SO_4 at 90 °C according to ref 3. After alkalization the solution was extracted twice with ether. Drying ($MgSO_4$) and evaporation of the solvent gave 56.1 g (97%) of crude product (Z/E ratio 60:40). Recrystallization 5 times from toluene afforded 19.1 g (33%) of pure **5Z**: mp 130.5–131.5 °C (lit.[3] 131–131.5 °C); UV max 248 nm (ϵ 19 700).

The mother liquors from the last four recrystallizations were combined and evaporated to yield 25.0 g (43%, Z/E ratio 33:67, i.e., 58 mmol of **5E**). The residue and 58 mmol of picric acid were dissolved in 500 mL hot ethanol. After cooling the precipitate was collected and recrystallized from ethanol to give 24.2 g (24% overall yield) of pure **5E** picrate: mp 144–146 °C. Anal. Calcd. for $C_{20}H_{15}BrN_4O_8$: C, 46.26; H, 2.91; Br, 15.39; N, 10.79; O, 24.65. Found: C, 46.19; H, 2.95; Br, 15.58; N, 10.71; O, 24.67.

The base was liberated and recrystallized from toluene to give 8.8 g of isomerically pure **5E**: mp 102–104 °C; ^1H NMR($CDCl_3$) δ 3.8 (br, 1, OH), 4.27 (d, 2, allyl), 6.35 (t, 1, vinyl), 6.9–7.7 (m + AA'BB', 6, aromatic), 8.45 (dd, partly concealed, 1, 6-pyridyl), 8.50 (m, 1, 2-pyridyl); MS, m/z (relative intensity) 291/289 (M, 16/17), 273/271 (M – H_2O, 9/8), 262/260 (6/7), 248/246 (27/27), 210 (M – Br, 100), 193 (10), 192 (M – Br – H_2O, 17); UV max 225 nm (ϵ 15 500), 240 nm (shoulder, ϵ 14 600). Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; Br, 27.54; N, 4.83; O, 5.51. Found: C, 57.86; H, 4.21; Br, 27.48; N, 4.77; O, 5.65.

3-(4-Bromophenyl)-3-(3-pyridyl)propenal (3E and 3Z). (I) Alcohol **5E** (4.35 g, 15 mmol) was stirred with 13 g of MnO_2 in 100 mL of $CHCl_3$ for 2 h at room temperature. After filtration and evaporation the residue was recrystallized from i-Pr_2O/i-PrOH (15:1) to yield 3.3 g (77%) of **3E**: mp 93–94 °C; ^1H NMR ($CDCl_3$) δ 6.64 (d, 1, J = 8 Hz, vinyl), 7.15–7.85 (m + AA'BB', 6, aromatic), 8.70 (m, 1, 2-pyridyl), 8.74 (dd, 1, 6-pyridyl), 9.67 (d, J = 8 Hz, CHO); MS, m/z (relative intensity) 289/287 (M, 41/42), 208 (M – Br, 100); UV max 226 (ϵ 18 300), 248 (shoulder, 15 600), 15 600)8 min 218 (ϵ 18 100) nm. Anal. Calcd for $C_{14}H_{10}BrNO$: C, 58.36; H, 3.50; Br, 27.73; N), 4.86; 0, 5.55. Found: C, 58.26; H, 3.59; Br, 27.99; N, 4.86; O, 5.52.

(II) Amine **1E** (1.05 g, 3.3 mmol) was refluxed with 10 g of MnO_2 in 30 mL of $CHCl_3$ for 2 h. An additional 5 g of MnO_2 were added and the reflux was continued another 3 h. Filtration and evaporation afforded 0.94 g of a yellow oil, which was flash chromatographed on SiO_2 with EtOAc to give 0.75 g (79%) of **3E**. Recrystallization from i-Pr_2O gave 0.53 g (56%): mp 93–94 °C.

3Z: The analogous oxidations of **5Z** and **1Z** with MnO_2 have been described earlier:[3] mp 99–100 °C; ^1H NMR ($CDCl_3$) δ 6.72 (vinyl), 8.68 (m, 2-pyridyl), 8.85 (dd, 6-pyridyl), 9.63 (CHO); UV max 312 (ϵ 16 400), 236 (ϵ 13 000), min 273 (ϵ 9 500), 218 (ϵ 11 200) nm.

General Procedure for Reductive Amination (see Table I). Sodium cyanoborohydride (94 mg, 1.5 mmol) was added to a 10-mL methanolic solution of aldehyde **3Z** or **3E** (288 mg, 1 mmol), 10 mmol of dimethylammonium chloride (entries 1–8) or methylammonium chloride (entries 9–15), and x mmol of NaOH or y mmol of HCl (added as 1.0 M methanol solutions). The mixture was stirred with or without molecular sieves at room temperature for 0.5–20 h as noted in Table I. The solvent was evaporated (after filtration when molecular sieves was present), the residue treated with 10 mL of 2 M HCl and then the pH was adjusted to ca. 5. Extraction with ether, drying (Na_2SO_4), and evaporation of the ethereal layer afforded dialkylated products **7Z** (entries 9–14) and **7E** (entry 15) in the case of methylamine (see below). The aqueous phase was made alkaline (pH 10–11) and extracted twice with ether. Drying (Na_2SO_4) and evaporation gave the allylic amines **1Z** and **1E** (entries 1–8) or **2Z** and **2E** (entries 9–15) in yields and isomeric ratios as listed in Table I. The amines obtained were chromatographically (GC, TLC) and spectroscopically (NMR, MS, UV) identical with known compounds.[2a]

1Z: MS, m/z (relative intensity) 318/316 (M, 29/29); UV max 250 nm (ϵ 19 700); ^1H NMR ($CDCl_3$) δ 8.60 (dd, 6-pyridyl), 8.46 (m, 2-pyridyl).

1E: MS, same as **1Z**; UV max 219 nm (ϵ 21 900), 237 nm (shoulder, ϵ 18 100); ^1H NMR ($CDCl_3$) δ 8.53 (m, 2-pyridyl), 8.50 (dd, 6-pyridyl).

2Z: MS, m/z (relative intensity) 304/302 (M, 79/80); UV max 248 nm (ϵ 19 200); ^1H NMR ($CDCl_3$) δ 8.61 (dd, 6-pyridyl), 8.47 (m, 2-pyridyl).

2E: MS, same as **2Z**; UV max 220 nm (ϵ 20 800), 236 nm (shoulder, ϵ 18 800); ^1H NMR ($CDCl_3$) δ 8.54 (m, 2-pyridyl), 8.48 (dd, 6-pyridyl).

7Z; entry 9: yield 24%; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3, CH_3), 3.04 (d, 4, allyl), 6.27 (t, 2, vinyl), 6.9–7.6 (m + AA'BB', 12, aromatic), 8.45 (m, 2, 2-pyridyl), 8.61 (dd, 2, 6-pyridyl); MS, m/z (relative intensity) 577/575/573 (M, 2/4/2), 329/327 (18/18), 303/301 (21/30), 275/273 (12/17), 274/272 (20/21), 262/260 (32/33), 193 (100); UV max 251 nm (ϵ 37 600), min 227 nm (ϵ 26 400). Oxalate salt recrystallized from EtOH/MeOH: mp 185–187 °C. Anal. Calcd for $C_{31}H_{27}Br_2N_3O_4$: C, 55.96; H, 4.09; Br, 24.02; N, 6.32; O, 9.62. Found: C, 55.87; H, 4.16; Br, 24.19; N, 6.22; O, 9.73.

7E; entry 15: yield 22%; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3, CH_3), 3.10 (d, 4, allyl), 6.28 (t, 2, vinyl), 6.95–7.7 (m + AA'BB', 12, aromatic), 8.58 (m, 4, 2,6-pyridyl); MS, m/z (relative intensity) 577/575/573 (M, 5/8/5), 329/327 (19/20), 303/301 (24/31), 275/273 (12/17), 274/272 (20/21), 262/260 (32/33), 193 (100); UV max 220 nm (ϵ 33 200), 237 nm (shoulder, ϵ 29 300).

Entry 1. Reaction overnight according to the general procedure with 10 mmol of $Me_2NH_2^+Cl^-$, 0.5 mmol of HCl, and 1 mmol of **3Z**: The pH 10 extract gave 64 mg (20%) of amine **1Z**. The pH 4.5 extract gave 160 mg of a mixture of allylic alcohol **5Z** (30%) and methyl ether **6** (25%) according to GC–MS. **6**: MS, m/z (relative intensity) 305/303 (M, 20/21), 290/288 (M – CH_3, 8/8), 274/272 (M – OCH_3, 26/25), 273/271 (45/40), 262/260 (16/17), 224 (M – Br, 90), 193 (M – OCH_3 – Br, 94), 192 (M – MeOH – Br, 100). Cf. MS of **5Z**/**5E**.

Quenching Experiments (Table II and Figure 2). Aldehyde **3Z** or **3E** (0.5 mmol) was dissolved in 5 mL of methanol and rapidly mixed at $t = 0$ with a stirred methanol solution (total 5 mL) of 5 mmol of $Me_2NH_2^+Cl^-$ or $MeNH_3^+Cl^-$ plus $x/2$ mmol of NaOH (from 1.0 M methanol solution) at room temperature. At t min 1.0-mL aliquots (1/10) were withdrawn and quenched with 1.0-mL aliquots of a solution of 0.75 mmol of $NaBH_3CN$ in 10 mL of methanol. After reaction for ca. 1 h a portion of these mixtures was treated with 2 M HCl for some minutes. The samples were made alkaline with 2 M NaOH, extracted with ether, and analyzed on capillary GLC at 190–200 °C. The Z/E ratios are shown in Table II and Figure 2.

Europium-Induced Shifts in ^{1}H NMR. Solid tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium [Eu(fod)$_3$] was added in increments to a $CDCl_3$ (0.5 mL) solution of the aldehyde **3Z** or **3E** (70 mg). The gradient G (slope) was calculated for the vinyl, aldehyde, and 2-pyridyl protons from plots of induced chemical shift vs. (concentration of Eu(fod)$_3$/concentration of **3**) as described earlier.[10] The gradient ratios G(vinyl)/G(2-pyridyl) and G(vinyl)/G(2-aldehyde) are given in the text.

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Registry No. **1E**, 56775-89-4; **1Z**, 56775-88-3; **2E**, 60324-58-5; **2Z**, 60324-59-6; **3Z**, 77470-68-9; **3E**, 83049-64-3; **4**, 70263-43-3; **5Z**, 77470-73-6; **5E**, 91671-06-6; **5E** (picrate), 91671-07-7; **6**, 91671-10-2; **7Z**, 91671-08-8; **7E**, 91671-09-9; **8Z**, 91671-11-3; **8E**, 91671-12-4; **9Z**, 91671-13-5; **9E**, 91671-14-6; $NaBH_3CN$, 25895-60-7; $Me_2NH_2^+Cl^-$, 506-59-2; $MeNH_3^+Cl^-$, 593-51-1.

Acyclic Stereoselection. 22. Diastereofacial Selectivity in the Lewis Acid Mediated Reactions of Allylsilanes with Chiral Aldehydes and Enones[1]

Clayton H. Heathcock,* Syun-ichi Kiyooka, and Todd A. Blumenkopf

Department of Chemistry, University of California, Berkeley, California 94720

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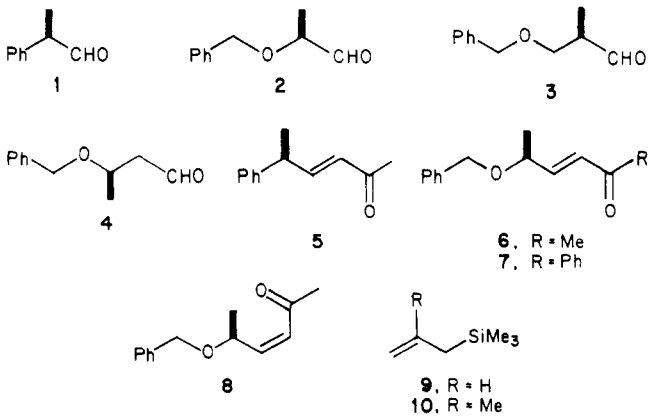
The Lewis acid mediated reactions of chiral aldehydes **1–4** and enones **5–8** with allylsilanes **9** and **10** have been investigated. With aldehyde **1** and enones **5–7**, modest diastereofacial preferences are seen, in the sense predicted by application of Felkin's model for asymmetric induction. Aldehydes **2–4** and enone **8** appear to react by way of chelated intermediates. With these four compounds, the diastereofacial preferences are rather large and are in the sense that is consistent with attack of the allylsilane on the least hindered face of the chelated intermediate. In the reactions of the trans and cis enones **6** and **8** with allyltrimethylsilane, a dramatic reversal of diastereofacial preference is observed; enone **6** gives a 84:14 ratio of products, while enone **8** provides a 10:90 mixture of the same products.

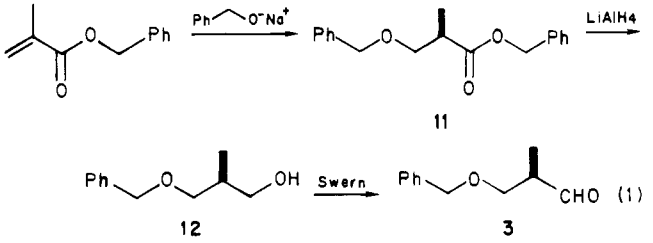
As a part of our investigation of the diastereoselectivity of carbon-carbon bond-forming reactions,[2] we have investigated the Lewis acid mediated reactions of allylsilanes with several chiral aldehydes and α,β-unsaturated ketones. In this paper, we report the results of that investigation.

Materials

The reactions of aldehydes **1–4** and enones **5–8** with allylsilane (**9**) and methallylsilane (**10**) in the presence of several Lewis acids were studied. Compound **1** may be



purchased from a commercial supplier,[3] although the material obtained is contaminated with about 15% acetophenone. However, this material may be readily purified (see Experimental Section). Compound **2** is prepared as previously reported.[4] Aldehyde **3** may be produced by the route summarized in eq 1. Addition of sodium benzyl



(1)

oxide to benzyl methacrylate gives **11**, which is reduced by lithium aluminum hydride to alcohol **12**. Swern oxidation[5] of the latter substance provides aldehyde **3**.[6]

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