Mechanistic Investigations on the Highly Stereoselective Allylation of Aldehydes with a Norpseudoephedrine Derivative

Lutz F. Tietze,* Christian Wulff, Christoph Wegner, Ansgar Schuffenhauer, and Kai Schiemann

Contribution from the Institut für Organische Chemie der Georg-August Universität, Tammannstrasse 2, D-37077 Göttingen, Germany

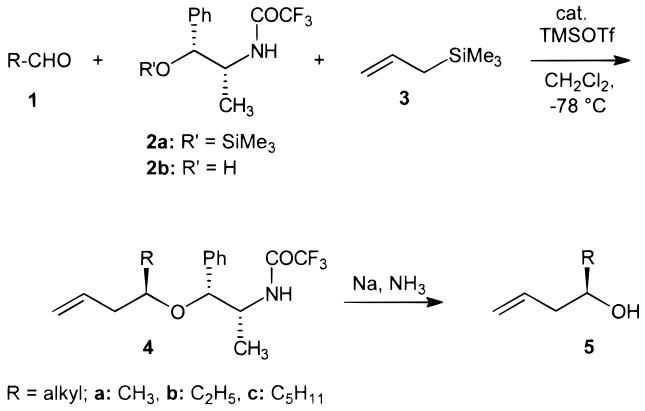
Received December 29, 1997

Abstract: Reaction of aliphatic aldehydes **1** and allylsilane **3** at −78 °C in the presence of the norpseudoephedrine derivative **2a** and catalytic amounts of trifluoromethanesulfonic acid trimethylsilyl ester gives the homoallylic ethers **4** with >98% diastereoselectivity. The ethers **4** can be transformed into the corresponding homoallylic alcohols **5** having an enantiomeric excess >98% using sodium in liquid ammonia. On-line NMR spectroscopy indicates that the mixed acetal **7** and the oxazolidinium ion **12** are intermediates in the formation of **4**. At higher temperature proton transfer occurs to give the oxazolidinium ion **18**, which does not react with allylsilane, but gives the oxazolidine **17** on aqueous workup. Protonation of **17** with trifluoromethanesulfonic acid leads to **18** but not to the oxazolidinium ion **12**. Thus, an allylation starting from **17** is not possible.

The allylation of aliphatic aldehydes **1**[1] with allylsilane **3** in the presence of the norpseudoephedrine derivative **2a** or *ent*-**2a** and catalytic amounts of trifluoromethanesulfonic acid trimethylsilyl ester (TMSOTf) is a very powerful procedure for the synthesis of enantiopure homoallylic alcohols **5** (Scheme 1).[2,3] Under these conditions nearly all aliphatic aldehydes can be transformed into the corresponding homoallylic ethers **4** with a selectivity of >99:1. Subsequent reductive removal of the chiral auxiliary gives the enantiopure homoallylic alcohols **5** together with the oxazolidine **17** as a side product. In similar fashion, ketones such as ethyl methyl ketone can be transformed into the corresponding tertiary homoallylic ethers with an astonishing diastereoselectivity (ds) = 96:4. However, in this case, the opposite configuration of the newly formed stereogenic center is found and the formation of an oxazolidine as a byproduct is not observed.[4]

The high stereocontrol in these reactions is quite surprising because the key bond-forming step takes place in an acyclic system and chelation can be excluded due to the use of the monodentate Lewis acid TMSOTf for aldehydes and the Brønsted acid trifluoromethanesulfonic acid (TfOH) for ketones. In this paper, we describe our investigations on the mechanism of the allylation of aldehydes using on-line NMR spectroscopy and model reactions of possible intermediates. In addition, the influence of the catalyst and the reaction temperature on the selectivity and the yield of the allylation are described.

Scheme 1



R = alkyl; **a:** CH_3, **b:** C_2H_5, **c:** C_5H_{11}

For the allylation of aldehydes **1**, it can be assumed that at first an oxenium ion (**6**) is formed, which reacts with the norpseudoephedrine derivative **2a** to give the mixed acetal **7** (Scheme 2).

This can undergo a cyclization to yield the oxazolidinium ions **11** or **12** either via formation of the oxenium ion **9** and **10**, respectively, or by direct substitution of **7**. The final step is the irreversible substitution of the allylsilane **3** at C-3 of **11** or **12** to give the homoallylic ether **4** with inversion of configuration of the stereogenic center as in **11** or **12**, which is in agreement with the experimental results. The high stereoselectivity in the synthesis of **4** makes it quite unlikely that a direct addition of **3** to **9** or **10** takes place to give **4**. Furthermore, we assume that **12**, not **11**, is the intermediate in the described process; two facts led to this assumption. First,

(1) (a) Tietze, L. F.; Dölle, A.; Schiemann, K. *Angew. Chem.* **1992**, *104*, 1366; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1372. (b) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164.

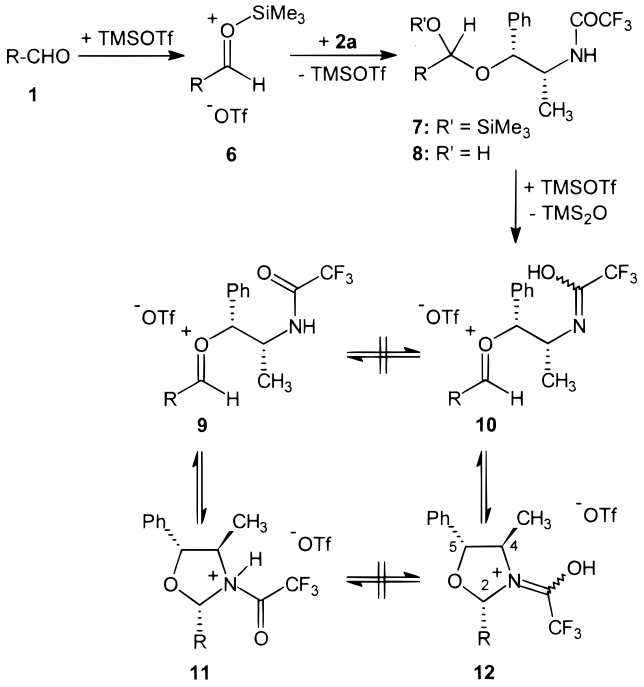
(2) For a review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(3) For selective allylations of aldehydes, see also: (a) Stürmer, R.; Hoffmann, R. W. *Synlett* **1990**, 759. (b) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am Chem. Soc.* **1990**, *112*, 2389. (c) Roush, W. R.; Banfi, L. *J. Am Chem. Soc.* **1988**, *110*, 3979. (d) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (e) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (f) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (g) Brückner, R.; Weigand, S. *Chem Eur. J.* **1996**, *2*, 1077. (h) Gauthier, D. E.; Carreira, E. M. *Angew. Chem.* **1996**, *108*, 2521. (i) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (j) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (k) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

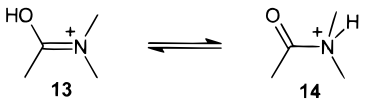
(4) (a) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851. (b) Tietze, L. F.; Wegner, C.; Wulff, C. *Synlett* **1996**, 471.

S0002-7863(97)04390-4 CCC: $15.00
Published on Web 04/28/1998

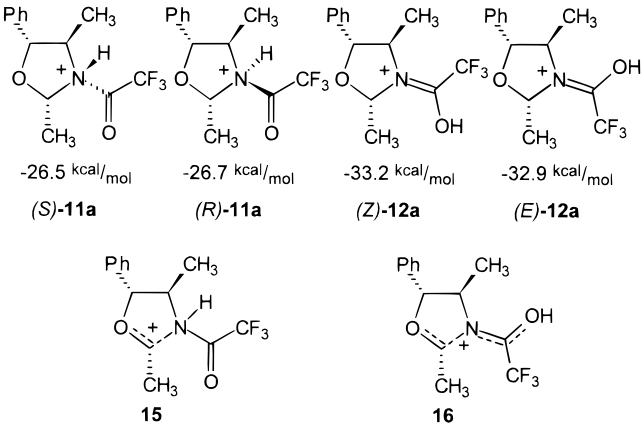
Scheme 2



Scheme 3



Scheme 4



it is known[5] that protonated amides **14** preferentially exist as their iminium-ion tautomers **13** (Scheme 3).

In addition, we have performed PM3-calculations, which show that the heat of formation of the iminium-ion tautomers (*E*)-**12a** and (*Z*)-**12a** is more than 6 kcal/mol lower than that of the corresponding protonated amides (*R*)-**11a** and (*S*)-**11a**. Thus, in the allylation a transition state of type **16** should be more favorable than that of type **15**. However, the calculations do not allow to distinguish between the two double bond isomers (*E*)-**12a** and (*Z*)-**12a** since they differ by only 0.3 kcal/mol (Scheme 4).

A second indication of the intermediacy of the oxazolidinium ion **12** is the occurrence of the oxazolidines **17** as side products

(5) Fraenkel, G.; Franconi, C. *J. Am. Chem. Soc.* **1960**, *82*, 4478.

Scheme 5

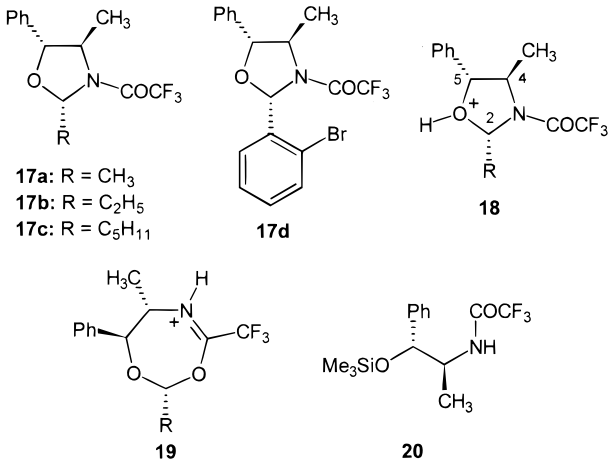


Table 1. Reaction of Aldehydes **1** with **2a** and TMSOTf

aldehyde **1**: R	TMSOTf (equiv)	react. time	products: yield (%) **2a**	**2b**	**17a**−**c**
a: CH_3	1.5	14 h	<1		**a**: 99
b: C_2H_5	0.1	30 s	51	49	**b**: <1
b: C_2H_5	0.1	5 min	30	70	**b**: <1
b: C_2H_5	0.1	15 min	21	79	**b**: <1
b: C_2H_5	0.1	60 min	16	79	**b**: 5
b: C_2H_5	1.1	60 min	12	<1	**b**: 88
c: C_5H_{11}	1.5	14 h	*a*	*a*	**c**: 46

[a] Yield not determined.

(Scheme 5). The relative configuration of **17a** has been confirmed by X-ray analysis and that of **17a**−**c** by NOESY spectra. Thus, it was thought that the stereochemistry of the resulting homoallylic ethers **4** might easily be explained by attack of allylsilane **3** at C-2 of the protonated *N,O*-acetal **12** by an S_N2 process. However, reaction of isolated **17a** with allylsilane **3** in the presence of a strong acid or TMSOTf did not lead to the desired homoallylic ether **4a**. To clarify this inconsistency and to get a better insight into the mechanism of the allylation, we performed on-line NMR spectroscopy of the reaction at various temperatures. In addition, the oxazolidines **17a**−**c** were prepared and investigated by NMR spectroscopy in the presence of acid and TMSOTf. For the synthesis of oxazolidines **17a**−**c**, the aldehydes **1a**−**c** were treated with the norpseudoephedrine derivative **2a** in dichloromethane in the presence of TMSOTf at −78 °C. Using more than 1 equiv of TMSOTf, the oxazolidines **17a**−**c** were formed in 99%, 88%, and 46% yields, respectively, as single diastereomers. However, with only 0.1 equiv of TMSOTf, the desilylated norpseudoephedrine derivative **2b** was the main product (Table 1). The ^{13}C NMR spectra of **17a**−**c** show two equilibrating species with a coalescence temperature of about 25 °C. At −78 °C separated signals were observed for the two isomers, whereas at 100 °C, only one resonance per carbon was found.

The formation of **2b** in the reaction of **1a** and **2a** with 0.1 equiv of TMSOTf could be explained by hydrolysis of **2a** during workup. However, this is unlikely since pure **2a** is stable under the reaction conditions. This would also not explain the increased yield of **2b** with prolonged reaction time. It must therefore be assumed that the mixed acetal **7** is formed as a first intermediate, which is stable in the absence of TMSOTf and forms **2b** via **8** during aqueous workup. A similar intermediate resembling **7** was recently isolated by Polt in the reaction of esters with DIBAH and (trimethylsilyl)imidazole.[6]

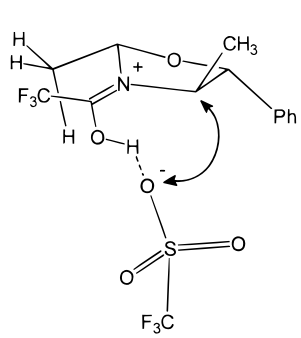
In the presence of excess TMSOTf **7** irreversibly gives the oxazolidinium ion **12**; this assumption is confirmed by our investigations showing that the yield of the isolated oxazolidine **17** corresponds directly to the amount of TMSOTf added (Table 1). Formation of **12** from **7** can proceed via silylation at the oxygen of the trimethylsilyloxy moiety followed by elimination of hexamethyldisiloxane and ring-closure either by a concerted process or via **10** as intermediate.[7] Deprotonation of the ion **12** during aqueous workup would give the oxazolidine **17**.

Other methods for the synthesis of the oxazolidines,[8] e.g., **17a**,**d** such as transacetalization of the dimethyl acetals of acetaldehyde or *o*-bromobenzaldehyde in the presence of catalytic amounts of the pyridinium salt of *p*-toluenesulfonic acid were less effective; only 12% of **17a** and traces of the unstable **17d** were obtained. Using the Lewis acid $BF_3{\cdot}OEt_2$ in toluene, no reaction occurred.

Having the pure oxazolidines **17a**−**c** in hand, we attempted to transform them into the homoallylic ethers **4** with allylsilane. As an example **17a** was reacted under various conditions; thus, different amounts of TfOH and a mixture of TfOH and TMSOTf with and without hexamethyldisiloxane were employed. In all cases, **17a** was recovered unchanged. Finally, **17a** was added to a reaction mixture of hexanal and **2a** in the presence of TMSOTf followed by addition of allylsilane. Again **17a** was recovered unchanged together with the homoallylic ether **4c** derived from hexanal. From these experiments, it can clearly be deduced that oxazolidines **17** are not intermediates in the described allylation of aldehydes. However, there is of course the possibility that both the oxazolidines and the homoallylic ethers are formed from the same intermediates. Therefore, the behavior of the oxazolidine **17a** in the presence of 1 equiv of TfOH and TMSOTf was studied by on-line ^{13}C NMR spectroscopy at −78 °C. In the presence of TMSOTf, the carbon resonances did not change, but a significant shift of the resonances was observed using TfOH. The signals of C-5 of **17a** were shifted upfield by about 2 ppm from $\delta = 85.68$ to 83.59 (major amide isomer) and from $\delta = 84.25$ to 82.24 (minor amide isomer) and those of C-2 by 0.44 ppm upfield from $\delta =$ 88.56 to 88.12 (major amide isomer) and downfield by about 1 ppm from $\delta = 86.98$ to 87.94 (minor amide isomer). In contrast, the C-4 signals were only slightly changed from $\delta =$ 60.16 to 59.98 (major amide isomer) and from $\delta = 61.51$ to 61.99 (minor amide isomer). The ^{13}C resonances observed for the $COCF_3$ group are nearly identical with those of the oxazolidine **17a**.

This clearly indicates that in the reaction of **17a** with TfOH neither **11** nor **12** was formed, and the protonation must have taken place at the ring oxygen to give **18**. A nucleophilic substitution at C-2 of the protonated oxazolidine **18** with allylsilane **3** to give **4** seems not to be possible under the reaction conditions, presumably due to the low activity of the hydroxyl moiety as a leaving group. Thus, the ring oxygen and not the carbonyl oxygen or the nitrogen seems to be the position of the highest basicity in **17**. Indeed, the reduced nucleophilicity of the carbonyl oxygen is an essential requirement for the allylation of the aldehydes, since reaction of **1** and **2** having an *N*-acetyl instead of the *N*-trifluoroacetyl moiety did not lead to the desired product.[4b]

Scheme 6



CIP-12 **CIP-18**

To prove the hypothesis that the oxazolidinium ion **12** is the intermediate which leads to the homoallylic ethers **4**, ^{19}F and ^{13}C NMR spectra were taken on reaction mixtures containing 2.0 equiv of acetaldehyde, 1.0 equiv of **2a**, and 1.0 equiv of TMSOTf at −78 °C in CH_2Cl_2/CD_2Cl_2. In the ^{19}F NMR spectra, two strong resonances of identical intensity at $\delta =$ −75.14 and −75.31 were observed in addition to the signals of the oxazolidine **17a** at $\delta = -69.81$ and $\delta = -70.80$, of **2a** at $\delta = -75.59$, of TMSOTf at $\delta = -77.11$ and of TfOH (small signal) at $\delta = -78.46$. We assume that these new signals correspond to the two trifluoromethyl groups of the oxazolidinium salt **12**. This was confirmed by the ^{13}C NMR data with signals at $\delta = 50.90$ for C-4, $\delta = 78.00$ for C-5, $\delta = 94.85$ for C-2, and $\delta = 115.1$ as well as $\delta = 153.3$ for the $COCF_3$ group. These signals are clearly different from those found for **18**. It can also be excluded from these data that the observed intermediate is the *O*-silyl oxonium triflate derived from **7**, since simple monosilyl acetals[6] show resonances at around $\delta = 100$ for the acetal carbon and for the oxonium ion a downfield shift should be found. This is not in accordance with the signal at $\delta = 94.85$ observed in the ^{13}C NMR spectrum of the reaction mixture. In addition, the oxonium ion of **7** would not lead to the oxazolidine **17** by quenching with triethylamine.

The observed chemical shift values of **12** and **18** are worthy of comment. A comparison of the ^{13}C NMR shift values of trialkylamines and of the corresponding tetraalkylammonium bromides shows that the resonances of the α-carbons of the ions appear downfield ($\Delta\delta = 3-5$ ppm), those of the β-carbons upfield ($\Delta\delta = 6-8$ ppm) and those of the γ-carbons downfield again ($\Delta\delta = 1-2$ ppm).[9] Therefore, a protonation of the nitrogen or oxygen as in **11**, **12**, and **18** should lead to a strong downfield shift of the resonances of the α-carbons, whereas for the β-carbons a strong upfield shift should be observed. However, such an observation would only be true for separated ion pairs. For contact ion pairs, the opposite is found due to the effect of the anion[10] as described by Pattaroni and Lauterwein[10a] for a similar problem. Thus, we assume for **12** and **18** the existence of the contact ion pairs **CIP-12** and **CIP-18**, which is in accordance with the NMR data (Scheme 6).

Compound **12** can exist as two double-bond isomers. Although PM3 calculations on the individual separated ions did not allow us to rule out one of the two double-bond isomers, the NMR data clearly indicate that the contact ion pair exists preferentially as a single isomer since only one set of signals is

(6) Sames, D.; Liu, Y.; DeYoung, L.; Polt, R. *J. Org. Chem.* **1995**, *60*, 2153.

(7) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(8) (a) Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600. (b) Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem.* **1989**, *101*, 65; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67.

(9) Hart, J. D.; Ford, W. T. *J. Org. Chem.* **1974**, *39*, 363.

(10) (a) Pattaroni, C.; Lauterwein, J. *Helv. Chim. Acta* **1981**, *64*, 1969. (b) Ogino, J.-I.; Suezawa, H.; Hirota, M. *Chem. Lett.* **1983**, 889. (c) Ilczyszyn, M.; Ratajczak, H.; Skowronek, K. *Magn. Reson. Chem.* **1988**, *26*, 445. (d) Andres, C.; Delgado, M.; Pedrosa, R. *Synth. Commun.* **1992**, *22*, 829. (e) Paz-Sandoval, M. A.; Santiesteban, F.; Contreras, R. *Magn. Reson. Chem.* **1985**, *23*, 428.

Table 2. Allylation of Aldehyde **1a** with Different Catalysts and at Different Temperatures

catalyst	temp (°C)	time	yield (%) 2a	2b	4a	17a
TMSOTf	−78	30 s[a]	14	15	67	4
TfOH	−78	30 s[a]	15	62	23	<1
TMSOTf	−78	5 min[a]	17	15	65	3
TfOH	−78	5 min[a]	17	51	32	<1
TMSOTf	−78	12 h[b]	26		66	8
$TMSB(OTf)_4$	−78	12 h[b]	12		65	23
TMSOTf	−60	12 h[b]	41		11	48
$TMSB(OTf)_4$	−60	12 h[b]	30		19	51
TMSOTf	−50	12 h[b]	51		7	42
$TMSB(OTf)_4$	−50	12 h[b]	24		21	55

[a] Time after the addition of allylsilane **3** (2.0 equiv); before addition of **3**, **1a** (2.0 equiv), **2a** (1.0 equiv), and the catalyst (0.1 equiv) were kept for 1 h. [b] Total reaction time.

found. Due to the strong shielding of C-4, it is most reasonable that the configuration of the double bond is *E*. Thus, H-bonding to the triflate anion leads to an interaction between the triflate and the C-2 methyl group, resulting in a shielding of C-4 with the consequence of an upfield shift of the C-4 resonance. In **18**, the situation is different because the phenyl and methyl group at C-5 and C-2, respectively, are situated on the same side of the molecule. Protonation can now take place from the α- or *β*-side, influenced by a 1,3 or a 1,2 interaction. However, in both cases a similar interaction between the triflate and the two α-substituents would exist, resulting in a similar shielding of C-2 and C-5, which is observed experimentally.

Though in the formation of **4** the intermediacy of the ion **12** seems to be most likely, it is also possible that the oxygen of the carbonyl moiety of the trifluoroacetamide group in **10** acts as a nucleophile to give a seven-membered ion **19**. The ion **19** cannot be excluded on grounds of the NMR data. If it is assumed that the formation of the seven-membered ring occurs diastereoselectively, then the observed stereocontrol in the allylation step could be explained. However, the preferred formation of a seven-membered over a five-membered ring as well as a diastereoselective cyclization to **19** is highly unlikely. Furthermore, the diastereoselective formation of **17** from **19** cannot easily be explained.

For the allylation of aldehydes, TMSOTf and $TMSB(OTf)_4$[11] were used as catalysts. Both compounds can contain considerable amounts of TfOH. Therefore, the reactions were also performed with pure TfOH. The results clearly show that TfOH is much less suitable as a catalyst than TMSOTf. In addition, the use of the very strong Lewis acid $TMSB(OTf)_4$ gives no advantage over TMSOTf which is commercially available and therefore preferable (Table 2).

The time and temperature dependence of the transformation revealed two important features. First, the homoallylic ethers **4** are formed very fast after the addition of the allylsilane **3**. Second, with increasing temperature, the yield of the homoallylic ethers **4** decreases dramatically whereas the amount of the oxazolidine **17** increases. This indicates that an irreversible proton transfer in **12** occurs to give **18** at higher temperatures, whereas at temperatures below −80 °C, this process must be rather slow.

The experimental results and the on-line NMR investigations allow us to now present the following mechanism for the highly stereoselective allylation of aldehydes **1** to give the homoallylic ethers **4**. In the first step, the oxenium ion **6** is formed from **1** in the presence of TMSOTf which reacts with **2a** to give the mixed acetal **7** and 1 equiv of TMSOTf. In the next step, **7** is transformed into the oxazolidinium salt **12** using 1 equiv of TMSOTf. At temperatures above −80 °C, proton transfer in **12** occurs to give the isomeric oxazolidinium ion **18** as a single diastereomer as detected by on-line NMR spectroscopy. The ion **18** does not react with the allylsilane **3**, but yields the oxazolidine **17** after aqueous workup. At temperatures below −80 °C, **12** is stable and reacts with the allylsilane **3** to give the desired homoallylic ether **4** in an S_N2-type fashion with inversion of the configuration at C-2 of **12**. In addition, 1 equiv of TMSOTf is formed, so that TMSOTf is necessary only in catalytic amounts. The lower selectivity of the allylation of aromatic aldehydes **1** (R = Ar) using this method may be due to a stabilization of the open oxenium ion **10**, which is in equilibrium with **12** being controlled by the character of the substituent R and which reacts with **3** in a nonstereoselective fashion.[12] Also of interest is the result that the diastereoselectivity of the allylation decreases dramatically (52−78% dr) using the ephedrine derivative **20**.[1] Thus, the highly stereoselective formation of **12** is controlled by both stereogenic centers C-1 and C-2 in **2a**. This is in clear contrast to the allylation of ketones,[4] where such a dependence was not observed. Due to this fact and the opposite configuration of the newly formed stereogenic center in the resulting homoallylic ether, the intermediacy of an oxazolidinium ion of type **12** is very unlikely in the allylation of ketones. We are aware that the proposed mechanism is somehow provocative since it assumes that at low temperature the S_N2 displacement at **12** by allyl silane is faster than the proton transfer. However, all obtained facts are in clear accordance with this mechanism.

Experimental Section

Instrumentation. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV. UV−vis spectra [λ_{max}, nm (log ϵ)] were taken in CH_3CN. IR spectra were recorded as KBr pellets or as films. Melting points are corrected.

Materials. All solvents were dried and distilled prior to use. All compounds were obtained enantio- and diastereomerically pure. Transformations and NMR studies were performed in flame-dried glassware under inert gas atmosphere.

General Procedure I. Preparation of Oxazolidines 17. To a solution of **1** (2.00 mmol) and **2a** (1.00 mmol) in CH_2Cl_2 (5 mL) was added TMSOTf (1.10 mmol) dropwise with stirring at −78 °C, and stirring was continued for 1−24 h at −78 °C. The reaction was quenched by addition of aqueous triethylamine (2.00 mL) at −78 °C. The solution was washed with water (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 3.0 mL). The combined organic phases were dried (Na_2SO_4), the solvent was evaporated, and the crude product was purified by column chromatography on silica gel (*tert*-butyl methyl ether/petroleum ether, 1:10).

General Procedure II. On-line NMR Studies of the Reaction Mixture. To a solution of **1** (2.0 equiv) and **2a** (1.0 equiv) in CH_2Cl_2 (450 μL) in an NMR tube were added carefully TMSOTf (1.0 equiv) and CD_2Cl_2 (150 μL) at −98 °C. Measurement of the spectra was started immediately at a temperature of −78 °C.

(2*S*,4*R*,5*R*)-2,4-Dimethyl-5-phenyl-3-(trifluoroacetyl)oxazolidine (17a). Reaction of **1a** and **2a** according to general procedure I gave 273 mg (99%) of **17a** as a white solid: mp 40 °C; R_f 0.53 (*tert*-butyl methyl ether/petroleum ether, 1:3); $[\alpha]^{20}_D$ −11.0° (*c* 1.00, $CHCl_3$); UV 191 (4.222), 208 (3.779); IR (KBr) 3068, 3034, 1688; ^1H NMR

(11) Davis, A. P.; Jaspars, M. *Angew. Chem.* **1992**, *104*, 475; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 470.

(12) (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. A. *J. Org. Chem.* **1990**, *55*, 6107. (b) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. (c) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. (d) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089.

(200 MHz, $CDCl_3$) δ 1.43 (d, J = 6.0 Hz, 3 H), 1.66 (d, J = 5.1 Hz, 3 H), 4.10 (br, 1 H), 4.58 (br d, J = 6.4 Hz, 1 H), 5.55 (br, 1 H), 7.33−7.46 (m, 5 H); ^{13}C NMR (125.7 MHz, CD_2Cl_2, −78 °C), major amide isomer δ 16.7, 18.2, 60.2, 85.7, 88.6, 115.2 (q, $^1J_{CF}$ = 287 Hz), 127.0, 128.4, 128.8, 135.5, 154.7 (q, $^2J_{CF}$ = 38 Hz), minor amide isomer δ 13.39, 21.16, 61.51, 84.25, 86.98, 115.3 (q, $^1J_{CF}$ = 288 Hz), 126.9, 128.4, 128.8, 135.3, 154.4 (q, $^2J_{CF}$ = 38 Hz); ^{13}C NMR (50.3 MHz, $C_2D_2Cl_4$, 100 °C) δ 17.41, 20.78, 60.32, 86.28, 88.34, 116.1 (q, $^1J_{CF}$ = 288 Hz), 126.8, 128.8, 129.0, 137.4, 154.3 (q, $^2J_{CF}$ = 38 Hz); ^{19}F NMR (470.3 MHz, CH_2Cl_2/CD_2Cl_2 (3:1), −80 °C) δ −70.81 (major amide isomer), −69.82 (minor amide isomer); MS *m*/*z* 273 (2, M^+), 230 (6, $M^+ - C(CH_3)O$), 167 (100, $M^+ -$ PhCHO). Anal. Calcd for $C_{13}H_{14}F_3NO_2$ (273.3): C, 57.14; H, 5.16. Found: C, 57.23; H, 4.97.

(2*S*,4*R*,5*R*)-2-Ethyl-4-methyl-5-phenyl-3-(trifluoroacetyl)oxazolidine (17b). Reaction of **1b** and **2a** according to general procedure I gave 253 mg (88%) of **17b** as a colorless oil: R_f 0.54 (*tert*-butyl methyl ether/petroleum ether, 1:5); $[\alpha]^{20}_D$ −32.7° (*c* 0.75, $CHCl_3$); UV 191 (4.179), 209 (3.738); IR (film) 3090, 3068, 3036, 1686; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (br t, J = 8.2 Hz, 3 H), 1.43 (d, J = 7.5 Hz, 3 H), 2.05 (m, 2 H), 3.97 (m, 1 H), 4.53 (d, J = 8.0 Hz, 1 H), 5.49 (m, 1 H), 7.34−7.48 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$), major amide isomer δ 7.1, 18.0, 24.0, 60.6, 86.5, 92.3, 115.8 (q, $^1J_{CF}$ = 288 Hz), 127.0, 128.7, 129.1, 136.5, 155.5 (q, $^2J_{CF}$ = 38 Hz), minor amide isomer (different signals) δ 14.3, 28.2, 61.86, 85.53, 90.76; MS *m*/*z* 287 (0.4, M^+), 258 (100, $M^+ - CH_3CH_2$), 230 (51, $M^+ - CH_3CH_2CO$), 181 (57, $M^+ -$ PhCHO); EI HRMS *m*/*e* 287.1133, $C_{14}H_{16}F_3NO_2$ requires 287.1133.

(2*S*,4*R*,5*R*)-4-Methyl-2-pentyl-5-phenyl-3-(trifluoroacetyl)oxazolidine (17c). Reaction of **1c** and **2a** according to general procedure I gave 137 mg (46%) of **17c** as a colorless oil: R_f 0.58 (*tert*-butyl methyl ether/petroleum ether, 1:3); $[\alpha]^{20}_D$ −39.7° (*c* 0.75, $CHCl_3$); UV 209 (3.661); IR (film) 3068, 3036, 1688; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (br, 3 H), 1.20−1.60 (m, 6 H), 1.42 (d, J = 6.0 Hz, 3 H), 1.86 (br, 1 H), 2.12 (br, 1 H), 4.00 (br, 1 H), 4.53 (d, J = 7.8 Hz, 1 H), 5.50 (br, 1 H), 7.30−7.50 (m, 5 H); ^{13}C NMR (125.7 MHz, CD_2Cl_2, −78 °C), major amide isomer δ 13.9, 16.5, 22.2, 22.5, 31.3, 31.1, 60.5, 85.6, 91.2, 115.2 (q, $^1J_{CF}$ = 287 Hz), 127.1, 128.4, 128.9, 135.4, 154.6 (q, $^2J_{CF}$ = 38 Hz), minor amide isomer δ 13.9, 13.3, 21.8, 22.5, 30.0, 33.8, 61.9, 84.3, 89.5, 115.3 (q, $^1J_{CF}$ = 288 Hz), 127.0, 128.3, 128.8, 135.3, 154.6 (q, $^2J_{CF}$ = 38 Hz); ^{13}C NMR (50.3 MHz, $C_2D_2Cl_4$, 100 °C) δ 13.74, 17.21, 22.35, 23.28, 31.39, 33.36, 60.54, 86.39, 91.53, 116.1 (q, $^1J_{CF}$ = 288 Hz), 126.8, 128.8, 129.0, 137.3, 154.6 (q, $^2J_{CF}$ = 38 Hz); MS *m*/*z* 329 (0.2, M^+), 258 (100, $M^+ - C_5H_{11}$), 230 (25, $M^+ - C_6H_{13}O$); EI HRMS *m*/*e* 329.1602, $C_{17}H_{22}F_3NO_2$ requires 329.1603.

On-line ^{13}C NMR Study of the Protonation of 17a. To a solution of **17a** (50.0 mg, 180 μmol, 1.0 equiv) in CD_2Cl_2 (550 μL) in an NMR tube was added TfOH (17.0 μL, 180 μmol, 1.0 equiv) carefully at −78 °C, and a ^{13}C NMR spectrum of the mixture was immediately taken at −78 °C: ^{13}C NMR (125.7 MHz, CD_2Cl_2, −78 °C), major amide isomer δ 18.9, 19.7, 60.0, 83.6, 88.1, 114.9 (q, $^1J_{CF}$ = 285.9 Hz), 124.7, 126.5, 128.6, 135.8, 155.4 (q, $^2J_{CF}$ = 40.3 Hz), minor amide isomer (different signals) δ 15.5, 19.5, 62.0, 82.2, 87.9, 115.1 (q, $^1J_{CF}$ = 286 Hz), 155.3 (q, $^2J_{CF}$ = 41 Hz).

On-line ^{13}C and ^{19}F NMR Studies of the Reaction of 1a with 2a. For ^{13}C NMR studies, **1a** (18.0 μL, 310 μmol, 2.0 equiv), **2a** (50.0 mg, 160 μmol, 1.0 equiv), and TMSOTf (31.0 μL, 160 μmol, 1.0 equiv) were used. For ^{19}F NMR studies **1a** (5.3 μL, 76 μmol, 2.0 equiv), **2a** (12.0 mg, 38.0 μmol, 1.0 equiv), and TMSOTf (7.4 μL, 38 μmol, 1.0 equiv) were used: ^{13}C NMR (125.7 MHz, CH_2Cl_2/CD_2Cl_2, 3:1, −78 °C) δ 14.6, 19.5, 50.9, 78.0, 94.9, 115.0 (q, $^1J_{CF}$ = 287.5 Hz), 126.6, 128.1, 128.6, 136.5, 157.3; ^{19}F NMR (470.3 MHz, CH_2Cl_2/CD_2Cl_2, 3:1, −78 °C) δ −75.31, −75.14.

Acknowledgment. We thank the *Volkswagen Stiftung* and the *Fonds der Chemischen Industrie* for generous support.

JA974390+