Communications to the Editor

Enantioselective Synthesis of Tertiary Homoallylic Alcohols via Diastereoselective Addition of Allylsilanes to Ketones

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Received December 23, 1994

The addition of allylmetal species such as allylsilanes, allylboranes, or allylstannanes to aldehydes and ketones is a highly efficient and broadly used method for the synthesis of homoallylic alcohols.[1] In addition, homoallylic ethers may be obtained by a Lewis acid-promoted reaction of acetals with allylmetal compounds.[2] Homoallylic alcohols and ethers are important building blocks and have been widely used in the synthesis of natural products. Great effort has been put into the development of the enantioselective formation of these compounds using either chiral allylmetal species,[3] chiral acetals,[4] or quite recently also catalytic methods.[5] Thus, several highly selective methods are now known for the synthesis of enantiopure secondary homoallylic alcohols starting from aldehydes. In contrast, the selectivity in the allylation of ketones to give tertiary homoallylic alcohols is quite low,[6] and a feasible procedure does not exist.

Based on our work on the synthesis of acetal glycosides for highly selective anticancer agents,[7] we have recently shown that in a domino type reaction,[8] aliphatic aldehydes can be transformed into homoallylic ethers from which the corresponding homoallylic alcohols are obtained with an enantiomeric excess of >99% in nearly all examples investigated.[9] Thus, reaction of the aldehyde **1a** with the trimethylsilyl ether of (1*R*,2*R*)-*N*-(trifluoroacetyl)norpseudoephedrin (**2**) and trimethylallylsilane (**3**) in the presence of a catalytic amount of trimethylsilyl triflate

Scheme 1

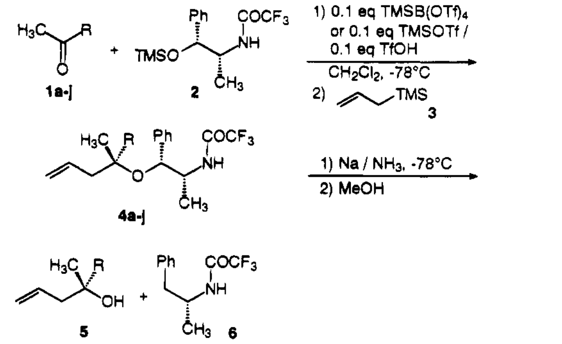

Table 1. Synthesis of Homoallylic Ethers **4a–j** from Aldehyde **1a** and Methyl Ketones **1b–j**

	R	yield of **4** (%)[a]	diastereomer ratio[b]	$[\alpha]^{20}_{D}$[c]	mp (°C)[d]	yield of **5** (%)
a	H[e]	*f*	>99:1[g]	−1.5	60	
b	CH_2CH_3	82 (89)	89:11[h]	+11.0	67	76
c	$(CH_2)_2C_6H_5$	63 (91)	91:9[h]	+31.0	100	92
d	$(CH_2)_2CH{=}CH_2$	73 (92)	91:9[h]	+22.7	62	
e	$(CH_2)_4CH_3$	79 (89)	88:12[h]	+17.7	67	
f	$(CH_2)_2OCH_2CH_3$[i]	64 (84)	86:14[h]	−15.0	59	
g	$(CH_2)_2OCH_2CH{=}CH_2$[i]	61 (87)	88:12[h]	−14.3	oil	
h	$(CH_2)_3COOCH_3$	58 (91)	88:12[h]	+12.5	oil	
i	$CH(CH_3)_2$	53 (87)	>95:5[g]	−4.5	113	85
j	$C(CH_3)_3$	22 (88)	91:9[g]	−4.7	156	

[a] The yields in parentheses are based on conversion. [b] Determined by ^{13}C NMR spectroscopy. [c] $c = 1$ in $CHCl_3$ solution of the mixture of diastereomers. [d] Recrystallized from *tert*-butyl methyl ether/petroleum ether. [e] The reaction was performed with TMSOTf as catalyst. [f] The crude product was cleaved to the homoallylic alcohol without further purification. [g] The major diastereomer has the (*R*) configuration. [h] The major diastereomer has the (*S*) configuration. [i] The reaction was performed with the (1*S*,2*S*)-norpseudoephedrin derivative *ent*-**2**.

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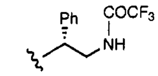
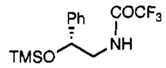
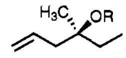
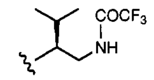
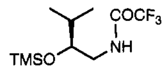
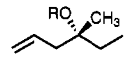
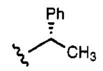
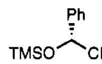
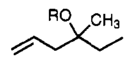
Table 2. Synthesis of Tertiary Homoallylic Ethers **8a–c** from Methyl Ethyl Ketone (**1b**) with the Chiral Trimethylsilyl Ethers **7a–c**

	R	TMS ethers 7[a]	homoallylic ethers 8	yield of 8 (%)	diastereomer ratio[b]	$[\alpha]_D^{20}$ [c]
a				90	89:11	−64.5
b				63	89:11	+23.8
c				25	64:36	

[a] **7a,b** were synthesized from enantiopure amino acids; **7c** was used in the racemic form. [b] Determined by ^{13}C NMR spectroscopy. [c] $c = 1$ in $CHCl_3$ solution of the mixture of diastereomers.

(Me_3SiOTf) gave **4a** with a diastereomeric excess of >99%, having the (*R*) configuration at the newly formed stereogenic center (Scheme 1).

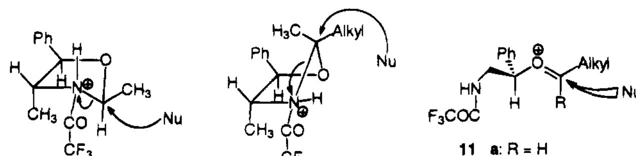
In this paper we describe the results of the transformation of the ketones **1b–j** using this procedure, which allows the synthesis of tertiary homoallylic ethers **4b–j** (Scheme 1) with a diastereomeric excess of up to >90% in about 90% yield (based on conversion, Table 1). Since Me_3SiOTf showed only a low reactivity as a catalyst for these reactions, we used $Me_3SiB(OTf)_4$.[10] However, quite recently we have found that a mixture of Me_3SiOTf and TfOH is even superior. In all transformations using the (1*R*,2*R*)-norpseudoephedrin derivative **2**, the formal *re*-face allylated ketones are the main products. Accordingly, with the (1*S*,2*S*)-norpseudoephedrin derivative *ent*-**2**, the *si*-face allylated ketones are obtained predominantly.

The selectivity of the transformations depends on the substituent R in **1b–j**: the α-unbranched alkyl methyl ketones **1b–h** gave 88:12–91:9 mixture of **4b–h** and their C-1′ epimers, and with isopropyl methyl ketone (**1i**), only the single diastereomer **4i** was formed. Unexpectedly, with *tert*-butyl methyl ketone (**1j**) to give mainly **4j**, the selectivity decreased. Aromatic ketones do not react, and α,*β*-unsaturated ketones give lower yields and selectivities. However, nonconjugated double bonds (as in **1d**) and aromatic ring systems (as in **1c**) are tolerated. Also, *β*-alkoxy ketones **1f,g** as well as ketoesters **1h** can be employed with good selectivity and yield (Table 1).

The absolute configuration of the obtained homoallylic ethers was deduced from a X-ray crystallographic analysis of the homoallylic ethers **4c,i**.

The homoallylic ethers **4** can easily be transformed into the homoallylic alcohols **5** by reductive cleavage of the benzyl moiety using sodium in liquid ammonia without isomerization, as shown for **4b,c,i** which gave **5b,c,i** in 76–92% yield, respectively, together with the amphetamine **6** (Scheme 1). However, it may be advantageous to use the homoallylic ethers for further transformations before deprotection.

The high selectivity in the allylations of aldehydes and ketones cannot be interpreted in a straightforward way since somehow the facial differentiation of the two reactions is opposed. In similiar transformations, an oxonium ion is usually assumed as an intermediate. However, for the allylation of aldehydes such as **1a**, it is not possible to explain the observed selectivity by an addition to an oxonium ion (**11a**). This



intermediate may exist in a stable conformation due to a 1,3-allylic strain,[11] as proposed by Houk[12] based on *ab initio* calculations, and the probable result would be the formation of homoallylic ethers with the opposite configuration. We therefore assume that an oxazolidinium ion (**9**) is formed as an intermediate, which is then opened in an S_N2 type reaction. On the other hand, the selectivity in the allylation of the ketones **1b–j** could be explained by the intermediate formation of the oxonium ion **11b**, assuming that here the formation of an oxazolidinium ion is restrained due to steric reasons. However, we have shown that on using the trimethylsilyl ether of 2-phenylethanol (**7c**) instead of the norpseudoephedrin derivative **2**, only a very low selevtivity is obtained, whereas with the amino alcohol derivatives **7a,b**, having also only one stereogenic center, a good selectivity was found (Table 2). This clearly indicates that the amide moiety is important in these reactions. We therefore assume that again an oxazolidinium ion (**10**) is an intermediate, but with an opposite configuration at C-1 and with a different conformation. In any case, further investigations are needed to explain these phenomena.

Acknowledgment. Financial support was provided by the Fonds der Chemischen Industrie.

Supplementary Material Available: Experimental procedures and characterization data for **4b–j** and **5b,c,i**, as well as details of the X-ray structure determination of **4c** and **4i** (19 pages); listing of observed and calculated factors for **4c** and **4i** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA944137Z

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