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Asymmetric Synthesis of Disubstituted C-Silylated Homoallylic Alcohols from Lithiated Allylic and Vinylic Sulfoximines

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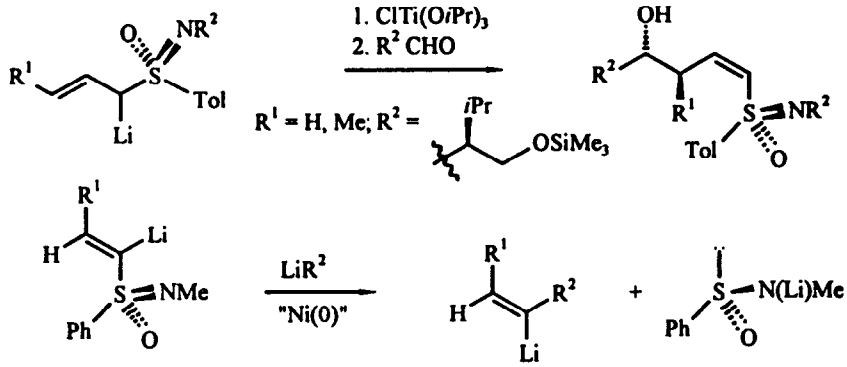
Abstract: Lithiation, titanation and hydroxyalkylation of allylic N-methyl sulfoximines **1-4** gave with ≥ 95% *de* the *anti-Z*-configurated homoallylic alcohols **5-9**. Lithiation of **6b** and **8b** with MeLi readily produced the lithiated vinylic sulfoximines (*Z*)-**12** and (*Z*)-**13**, respectively. Ni-catalyzed substitution of (*Z*)-**12** and (*Z*)-**13** with PhLi and 1,5-silyl migration yielded with ≥ 98% *de* the disubstituted C-silylated homoallylic alcohols (*Z*)-**14** and (*Z*)-**15**, respectively. (*Z*)-**15** thus obtained from (*Z*)-**13** had an *ee*-value of ≥ 98%.

Allylic[1-6] and vinylic[7-9] sulfoximines are attractive synthetic reagents because of the sulfonimidoyl group which is a chiral carbanion-stabilizing nucleofuge. This is exemplified by the highly selective hydroxyalkylation of titanated allylic sulfoximines leading to *anti*-homoallylic alcohols[4] and by the Ni-catalyzed substitution of α-lithiated vinylic sulfoximines yielding vinylic lithium compounds (Scheme 1).[8,10,11]

Scheme 1

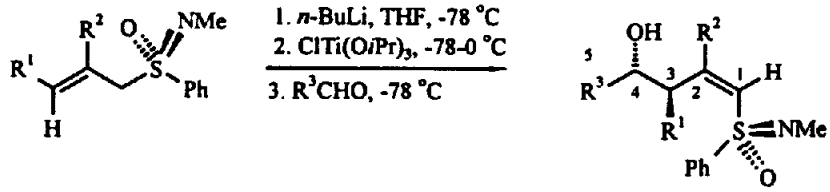


We describe here the asymmetric synthesis of disubstituted C-silylated homoallylic alcohols by the sequential hydroxyalkylation of a titanated allylic N-methyl sulfoximine, the Ni-catalyzed substitution of a lithiated vinylic sulfoximine[12] and a 1,5-O,C-silyl migration[13] (Schemes 2-5).

As educts served the allylic sulfoximines **1-4** which carry a methyl group at the N-atom. They are easily accessible from carbonyl compounds by the addition-elimination-isomerization route utilized previously.[1,6,14a] Thus *rac*-**1-4**, (*S*)-**2-4**, and (*R*)-**3** were prepared in 38-65%, 40-65%, and 52% overall yield from (±)-, (*S*)-, and (*R*)-S-lithiomethyl S-phenyl N-methyl sulfoximine, respectively, and *n*-propanal, isovaleraldehyde, phenyl acetaldehyde,[14a] and benzyl methyl ketone,[14a] respectively.[14b] The *E*/*Z*-isomers obtained in the case of **1**, **2** and **4** as 2.3:1, 9:1 and 1.7:1 mixtures, respectively, were separated by MPLC. Lithiation of the allylic sulfoximines[1-4] *rac*-(*E*)-**1-4**, (*S*)-(*E*)-**2-4**, and (*R*)-(*E*)-**3** with *n*-BuLi (THF, -78 °C) gave quantitatively the corresponding lithiated allylic sulfoximines[15] which were titanated with $ClTi(OiPr)_3$ (1.1 equiv., -78-0 °C) (Scheme 2). Treatment of the thus generated titanated allylic sulfoximines with benzaldehyde and isobutyraldehyde (2 equiv., -78 °C) led to the isolation of the homoallylic alcohols *rac*-**5-8**, (*S*)-**7-9** and (*R*)-**8**, respectively, in yields of 40-46% with a diastereomeric excess in each case of ≥ 95%.[16,17] Thus in the case of (*S*)-**7-9** and (*R*)-**8** of the possible eight diastereomers the one shown with the *anti*-*Z*-configuration was formed with high selectivity. These results

show that for the attainment of high stereoselectivity at least in the hydroxyalkylations of the titanated allylic sulfoximines described an additional chiral substituent at the N-atom (Scheme 1)[4] is not necessary.

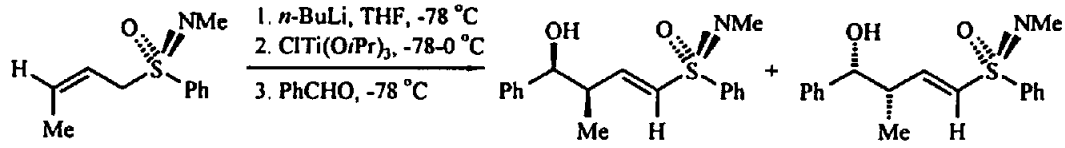
Scheme 2



(*E*)-**1**: R^1 = Me,	R^2 = H	**5a**: R^1 = Me, R^2 = H, R^3 = Ph,	46%, ≥ 95% *de*
(*E*)-**2**: R^1 = *i*Pr,	R^2 = H	**6a**: R^1 = Me, R^2 = H, R^3 = *i*Pr,	46%, ≥ 95% *de*
(*E*)-**3**: R^1 = Ph,	R^2 = H	**7a**: R^1 = *i*Pr, R^2 = H, R^3 = *i*Pr,	44%, ≥ 95% *de*
(*E*)-**4**: R^1 = Ph,	R^2 = Me	**8a**: R^1 = Ph, R^2 = H, R^3 = *i*Pr,	40%, ≥ 95% *de*
		9a: R^1 = Ph, R^2 = Me, R^3 = Ph,	46%, ≥ 95% *de*

Besides the homoallylic alcohol in all cases 40-50% of the starting allylic sulfoximine was recovered. Upon work-up of the reaction mixture with D_2O retrieved (*S*)-(*E*)-**2**, e. g., contained one D-atom in α-position. NMR-spectroscopic studies of the titanation of lithiated (*S*)-(*E*)-**2** with $ClTi(OiPr)_3$ in $[D]_8$-THF suggest that as in the case of the titanation of lithiosulfones[10] a diorganotitanium compound is formed preferentially besides $Ti(OiPr)_4$. Separation of the homoallylic alcohol and the allylic sulfoximine by chromatography or crystallization was tedious in the case of **5a**, **7a** and **8a**. Therefore the mixture of both was treated with $ClSiEt_3$ and the silyl ether readily isolated pure by chromatography in 85-94% yield besides the allylic sulfoximine.

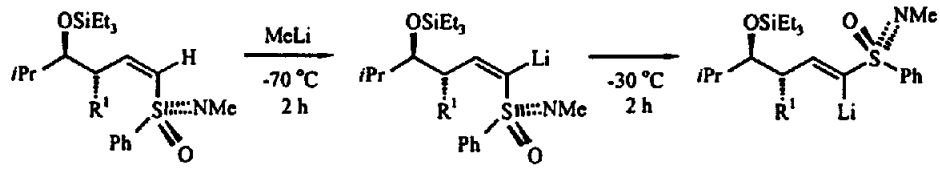
The hydroxyalkylation of (*Z*)-configurated titanated allylic sulfoximines is much slower than that of their (*E*)-isomers. Thus starting with a 3:1 mixture of *rac*-(*E*)-**1** and *rac*-(*Z*)-**1** only the former was partially consumed and a 1.7:1 mixture of both was recovered. Furthermore the hydroxyalkylation of titanated *rac*-(*Z*)-**1** gave a 2:1 mixture of the (*E*)-configurated homoallylic alcohols *rac*-**10** and *rac*-**11**, to whom we tentatively assign the *syn*-configuration, in 26% yield besides the allylic sulfoximine *rac*-(*Z*)-**1** in 40% yield.



(*Z*)-**1** **10** **11**

Lithiation of the vinylic sulfoximines[2,10,11] *rac*-**6b**, (*R*)-**8b** and *rac*-**8b** in α-position proceeded quantitatively with MeLi (1.4 equiv.) in ether at -70 °C under formation of the lithiated sulfoximines *rac*-(*Z*)-**12**, (*R*)-(*Z*)-**13** and *rac*-(*Z*)-**13**, respectively (Scheme 3). Deuterolysis of the lithiated (*Z*)-vinylic sulfoximine led to the recovery of the starting material containing deuterium in α-position in nearly quantitative yield in each case.

Scheme 3

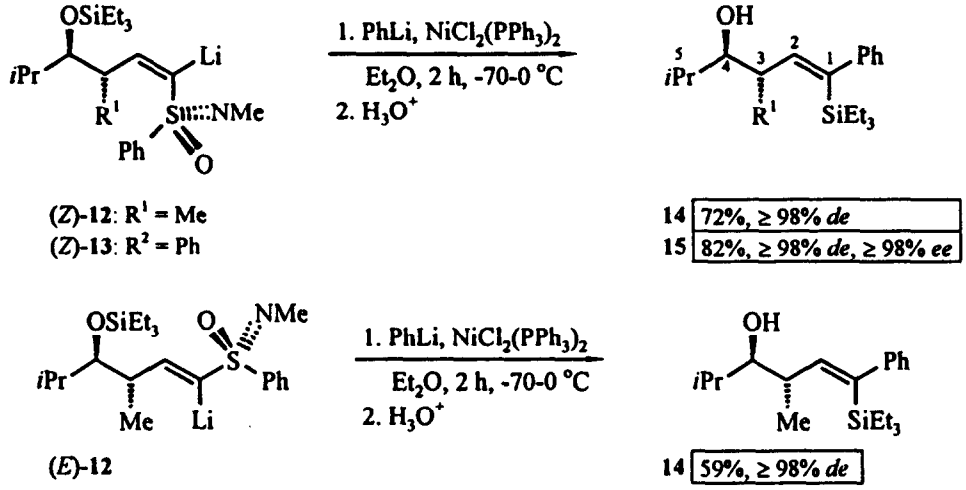


6b: R^1 = Me (*Z*)-**12** (*E*)-**12**
8b: R^1 = Ph (*Z*)-**13** (*E*)-**13**

Warming the solution of the lithiated sulfoximines *rac*-(*Z*)-12, (*R*)-(*Z*)-13 and *rac*-(*Z*)-13 to -30 °C for 2 h led to their quantitative isomerization to the (*E*)-configurated lithio sulfoximines *rac*-(*E*)-12, (*R*)-(*E*)-13 and *rac*-(*E*)-13, respectively, which gave upon protonation the corresponding (*E*)-configurated vinylic sulfoximines in high yield. This is in accordance with our previous finding that α-metallated vinylic sulfoximines suffer *Z*/*E*-isomerization at elevated temperatures.[8,10,11]

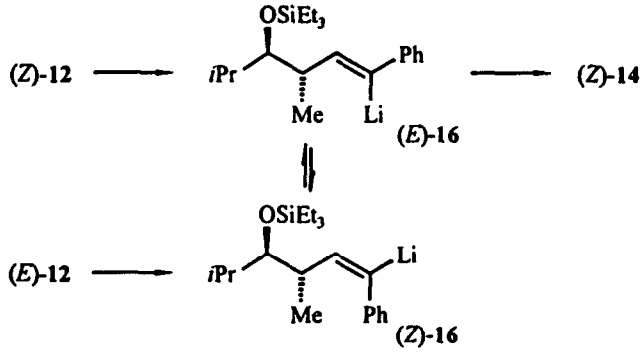
The Ni-catalyzed substitution of the lithiated vinylic sulfoximines[8,10,11] *rac*-(*Z*)-12, (*R*)-(*Z*)-13 and *rac*-(*Z*)-13 in ether with PhLi (2 equiv.) and $NiCl_2(PPh_3)_2$ (5 mol%) as precatalyst proceeded cleanly but, surprisingly, led to the isolation of the phenyl *and* C-silyl substituted diastereomerically pure homoallylic alcohols *rac*-(*Z*)-14, (*Z*)-15 and *rac*-(*Z*)-15, respectively, in good yields (Scheme 4). GC-analysis of *rac*-(*Z*)-15 and (*Z*)-15 on a per-methyl-ß-cyclodextrin column showed the latter to be also enantiomerically pure (≥ 98% *ee*).[19]

Scheme 4



Obviously, the vinylic lithium compound, which is formed initially (Scheme 5) presumably via a 1,2-metallate rearrangement[8,12] of a nickelate complex under inversion of configuration,[11] suffers a 1,5-O,C-silyl migration.

Scheme 5



Quite interesting in this context is the observation that the substitution of the (*E*)-configurated lithio sulfoximine *rac*-(*E*)-12 led under identical reaction conditions also to the (*Z*)-configurated homoallylic alcohol *rac*-(*Z*)-14 (Scheme 4). This result could be explained by assuming (1) an equilibrium between configurationally

labile *rac*-(*E*)-**16** and *rac*-(*Z*)-**16**[20] and (2) an intramolecular 1,5-O,C-silyl migration[13] which can only occur in *rac*-(*E*)-**16** because of steric reasons (Scheme 5).

From **5b-9b** through a Ni-catalyzed cross-coupling reaction with zincorganyls also monosubstituted homoallylic alcohols should be accessible.[8,9]

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