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Cycloadditions of Allylsilanes, Part 14.[1]

Enantiospecific Synthesis of Bicyclo[4.3.0]nonanes by Asymmetric [3+2] Cycloaddition of Chiral Allylsilanes

Hans-Joachim Knölker, Norbert Foitzik,* and *Oliver Schmitt*

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, 76131 Karlsruhe, Germany

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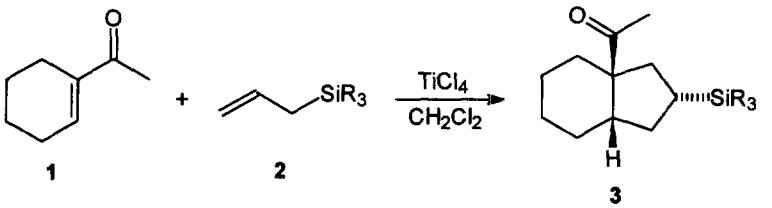
Abstract: The titanium tetrachloride promoted [3+2] cycloaddition of (*R*)-(1-phenylprop-2-enyl)trimethylsilane (*R*)-**4** (82% *ee*) and 1-acetylcyclohexene **1** provides an enantiospecific route to the bicyclo[4.3.0]nonane (+)-**6**.

Allylsilanes are extremely useful building blocks for stereoselective organic synthesis.[2] In addition to the classical Hosomi-Sakurai reaction[3] [3+2] and [2+2] cycloadditions can occur on Lewis acid promoted addition of allylsilanes and α,β-unsaturated carbonyl compounds.[4] For the [3+2] cycloaddition of 1-acetylcyclohexene **1** and allylsilanes **2** it was shown, that using sterically demanding substituents at the silicon atom the cyclopentane annulation becomes the major course of the reaction (Scheme 1).[5] The reaction is highly diastereoselective and provides in most cases exclusively the *anti* stereoisomers. Using a modified Fleming-Tamao oxidation[6] the silylcyclopentanes can be transformed to hydroxycyclopentanes with retention of stereochemistry.[7] Therefore, this chemistry has found numerous applications to the synthesis of carbocyclic five-membered ring systems.[8]



1 **2** **3**

Scheme 1

SiR_3	**3**, Yield [%]
$SiMe_3$	18
$SiPh_3$	51
Si*t*-$BuPh_2$	69
Si*i*-Pr_3	86

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For projected applications of this methodology to organic synthesis it is very important to achieve an asymmetric synthesis of cyclopentanes. Danheiser[8a] and Panek[8c] reported the diastereoselective synthesis of monocyclic cyclopentanes by [3+2] cycloaddition using chiral allyl- and crotylsilanes.[9] We wanted to demonstrate the feasibility of asymmetric induction for the construction of the bicyclo[4.3.0]nonane ring system previously obtained in its racemic form (Scheme 1).[5,8g] The palladium-catalyzed asymmetric cross-coupling of the α-(trimethylsilyl)benzyl-Grignard reagent with alkenyl bromides developed by Hayashi opens up an easy access to chiral allylsilanes.[10] Wohl-Ziegler bromination of benzyltrimethylsilane afforded α-(trimethylsilyl)-benzyl bromide, which was transformed into the corresponding Grignard reagent.[11] Cross coupling of α-(trimethylsilyl)benzylmagnesium bromide with vinyl bromide using 0.5 mol% bis(triphenylphosphine)nickel(II) chloride afforded the allylsilane **4** in its racemic form.[12] We envisaged to use chiral GC as a fast and accurate method for the determination of the enantiomeric excess of our chiral starting material. In fact, we were able to elaborate a complete base line separation of the two enantiomers of racemic **4** using a commercial peralkylated γ-cyclodextrin column.[13] The asymmetric catalytic cross coupling of α-(trimethylsilyl)benzylmagnesium bromide and vinyl bromide was achieved following Hayashi's procedure.[10] In the presence of 0.5 mol% of dichloro[(*R*)-*N*,*N*-dimethyl-1-{(*S*)-2-(diphenylphosphino)ferrocenyl}ethylamine]palladium(II),[14] (*R*,*S*)-**5**, at 0°C the allylsilane (*R*)-**4** was obtained in 82% *ee* as determined by chiral GC (Figure 1). The specific rotation of the allylsilane (*R*)-**4** was $[\alpha]_D^{20} = -51.9$ ($c = 2.5$, C_6H_6), which based on comparison with the value reported in the literature[10] would correspond to an *ee* of 80%.

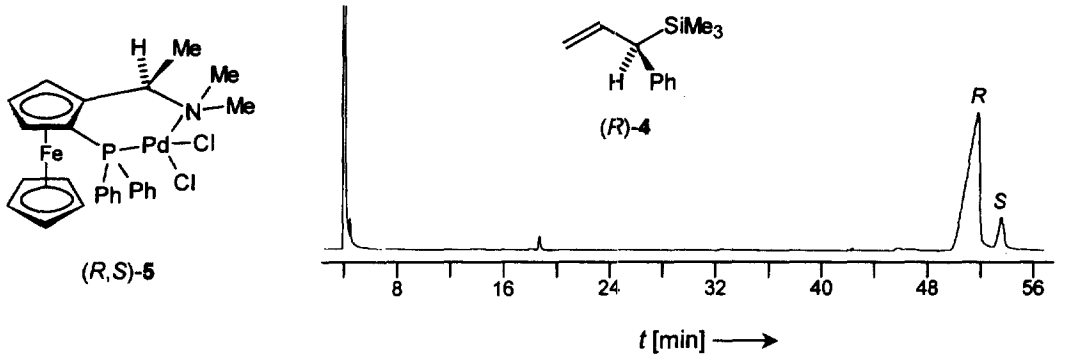
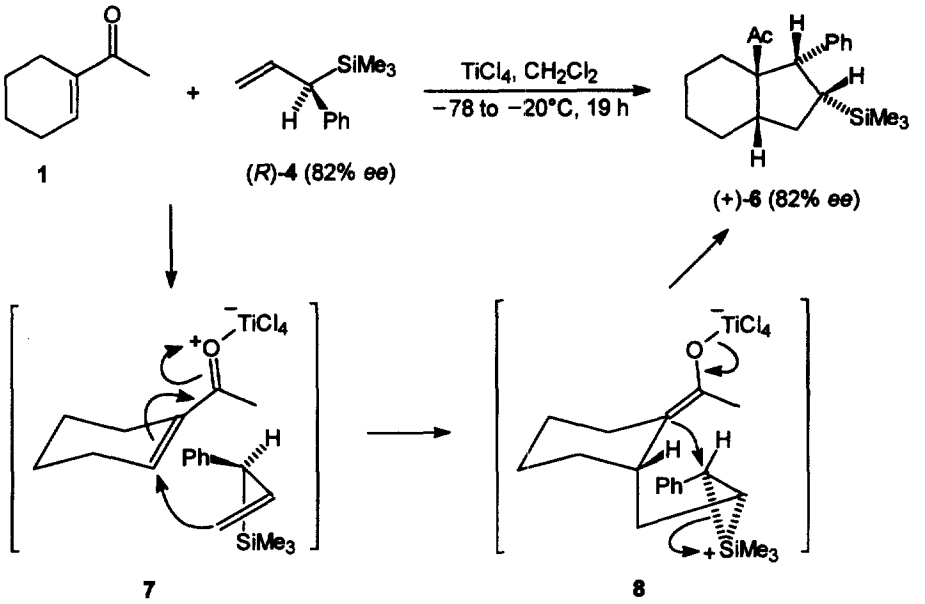


Figure 1. Chiral GC of the enantioenriched (82% *ee*) allylsilane (*R*)-**4**.[13]

The titanium tetrachloride promoted [3+2] cycloaddition of racemic allylsilane **4** and 1-acetylcyclohexene **1** using the standard reaction conditions[5,8g] provided the racemic bicyclo[4.3.0]nonane **6** in 25% yield. The product of the Hosomi-Sakurai reaction, 1-acetyl-2-allylcyclohexane, was isolated as a further product (40% yield) and separated by flash chromatography on silica gel. Based on our previous investigations 1-acetyl-2-allylcyclohexane was to be expected as the major product of the reaction with the present allylsilane.[5,8g] However, it was shown that the Hosomi-Sakurai reaction can be completely suppressed in favor of the [3+2] cycloaddition by using allylsilanes with bulky substituents at the silicon atom. At this stage we only wanted to see whether the enantiomeric excess of the starting material is transformed product. The two enantiomers of the bicyclo[4.3.0]nonane **6** can be separated by chiral HPLC on a permethylated β-cyclodextrin column, thus providing a reliable tool for the accurate determination of the enantiomeric excess of the product.[15]



Scheme 2

The [3+2] cycloaddition using the enantioenriched allylsilane (*R*)-**4** (82% *ee*) afforded the bicyclo[4.3.0]nonane **6** with 82% *ee* of the (+)-enantiomer as determined by chiral HPLC (Scheme 2, Figure 2).[16] Thus, using the appropriate reaction conditions the product exhibited the same enantiomeric excess as the starting material and only one diastereoisomer of **6** was formed. In analogy to previous work on allylsilane chemistry (compare ref.[2b,8a,9], *et loc. cit.*) **6** is thought to derive from an addition of the allylsilane *via* the synclinal arrangement **7**. Subsequent cyclization by intramolecular nucleophilic attack of the titanium enolate at the siliranium ion **8** would lead to the product. The stereochemistry is supported by the 12.0 Hz coupling of the benzylic proton.[16]
In conclusion, we could show that using the chiral non-racemic allylsilane **4** the [3+2] cycloaddition proceeds enantiospecific and generates chiral annulated cyclopentanes with four stereogenic centers.

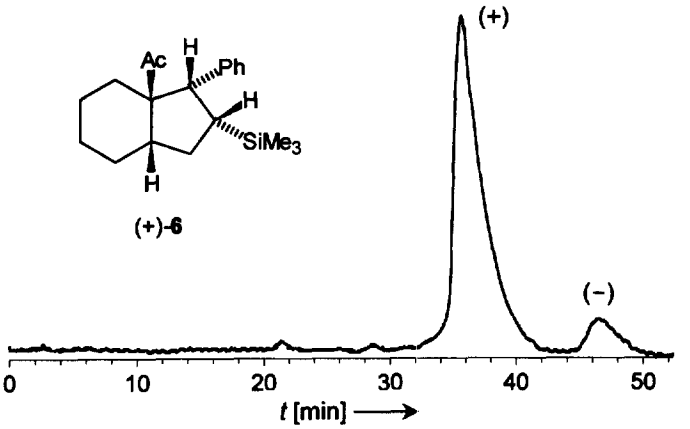


Figure 2. Chiral HPLC of the enantioenriched (82% *ee*) bicyclo[4.3.0]nonane (+)-**6**.[15]

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16. (+)-**6**: Colorless oil; yield: 23%; $[\alpha]_D^{20}$ = +23.7 (*c* = 1.5, $CHCl_3$); $[\alpha]_D^{20}$ = +21.6 (*c* = 0.9, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.20 (s, 9 H), 0.98 (m, 1 H), 1.42 (m, 3 H), 1.55 (m, 2 H), 1.62-1.75 (m, 4 H), 1.86 (s, 3 H), 2.06 (m, 1 H), 2.76 (m, 1 H), 2.99 (d, *J* = 12.0, 1 H), 7.09 (d, *J* = 6.9, 2 H), 7.20 (m, 3 H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –2.87 (3 CH_3), 20.14 (CH_2), 23.49 (CH_2), 24.23 (CH_2), 25.24 (CH_2), 27.16 (CH_3), 27.30 (CH), 27.92 (CH_2), 41.86 (CH), 59.00 (CH), 63.38 (C), 126.83 (CH), 127.88 (2 CH), 128.79 (2 CH), 139.65 (C), 213.57 (C=O); MS (25°C): *m/z* (%) = 314 (M^+, 13) 197 (100), 190 (15), 125 (9), 73 (44); HRMS: calcd. for $C_{20}H_{30}OSi$ (M^+): 314.2066, found: 314.2055.