Tetrahedron Letters 47 (2006) 2319–2321

Tetrahedron Letters

A method for the catalytic enantioselective synthesis of 6-silylated 2-cyclohexenones

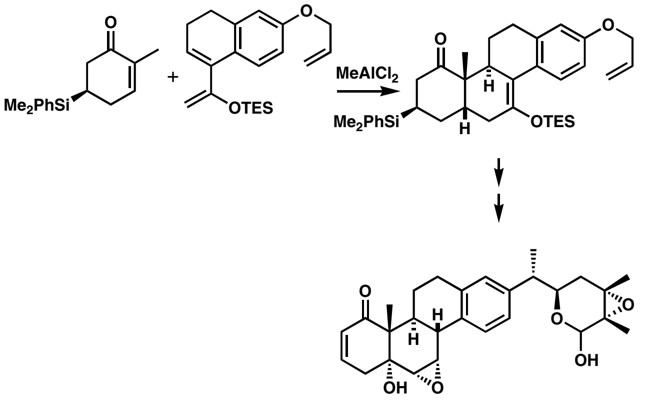
Min Ge and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138, USA

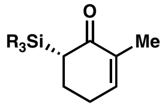
Received 19 January 2006; accepted 2 February 2006
Available online 20 February 2006

Abstract—6-Silylated-2-cyclohexenones can be synthesized enantioselectively by hydrosilylation of the corresponding diazo-2-cyclohexenone in the presence of a chiral Rh(II) catalyst.

We recently described an enantioselective total synthesis of nicandrenones (e.g., NIC-1), which a key step was a Diels–Alder reaction involving a chiral 5-silylated-2-methyl-2-cyclohexenone as the dienophilic component, as shown below.[1] As a result of this study we became interested in the question of whether a 6-silylated-2-methyl-2-cyclohexenone, for example **1**, could serve the same purpose. In turn, this raised the issue of how to synthesize compounds such as **1** enantioselectively and conveniently. Our initial research in this area is described herein.



NIC-1



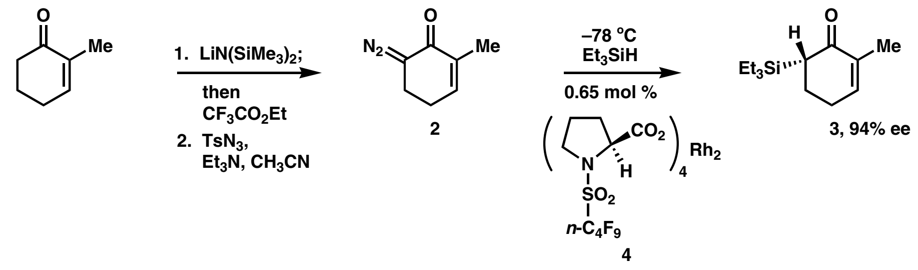
1

Previous studies have shown that simple α-silylated ketones can be prepared by silylation of the α-lithio derivative of a chiral *N*-amino α-methoxymethylpyrrolidine derivative of the ketone (*S*-, or *R*-AMP hydrazone).[2,3] We elected to pursue a different approach to the synthesis of chiral **1** that did not depend on the use of an expensive, non-recoverable chiral controller. Specifically, we investigated the reaction of an α′-diazo-α,β-enone with a trisubstituted silane using catalysis by a chiral Rh(II) carboxylate complex. We screened several (*S*)-*N*-sulfonylproline–Rh(II) complexes as catalysts for the reaction of 6-diaza-2-methyl-2-cyclohexenone with various silanes. Davies et al. had previously shown that this class of catalysts can be used for the conversion of achiral methyl allyldiazoacetate esters to chiral α-silylated esters.[4] After considerable experimentation, a fairly efficient catalytic enantioselective process was developed as summarized in Scheme 1. We used the Danheiser modification of Regitz's diazotransfer reaction[5] to convert 2-methyl-2-cyclohexenone to the 6-diazo derivative. Deprotonation of 2-methyl-2-cyclohexenone in THF at −78 °C followed by reaction of the resulting enolate with ethyl trifluoroacetate produced the α′-trifluoroacetylated derivative of the starting α,β-enone, which upon reaction with *p*-toluenesulfonyl azide and triethylamine in CH_3CN solution at 23 °C for 8 h gave the α′-diazo-α,β-enone **2** (for detailed conditions

---

* Corresponding author. Tel.: +1 617 495 4033; fax: +1 617 495 0376; e-mail: corey@chemistry.harvard.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.014

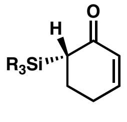


Scheme 1. Enantioselective synthesis of 6-(*S*)-triethylsilyl-2-methyl-2-cyclohexenone (**3**) by catalytic hydrosilylation of α-diazoketone **2**.

see Ref. 5b). Slow addition of the α,β-enone **2** to a solution of 2.6 equiv of triethylsilane and the catalyst, *N*-nonafluorobutanesulfonylproline (Nf-proline)–Rh(II) complex (**4**, Nf-proline$_4$ Rh$_2$, 0.65 mol %) in CH_2Cl_2 at −78 °C gave (+)-(*S*)-6-triethylsilyl-2-methyl-2-cyclohexenone **3** in 70% yield and 94% ee (for experimental details see Ref. 6). In a similar way the dextrorotatory *tert*-butyldimethylsilyl analog of **3** was synthesized in 80% ee. The absolute configuration of this product was determined to be *S* by hydrogenation (1 atm H_2, Pd–C, MeOH) to 2-*tert*-butyldimethylsilylcyclohexanone, $[\alpha]_D^{23}$ +150 (*c* 0.45, $CHCl_3$) by comparison with the known levorotatory *R*-enantiomer.[2b]

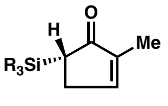
We studied a number of different Rh(II) N-sulfonylated proline salts to determine the optimal group on nitrogen. Mesitylsulfonyl-, pentafluorobenzenesulfonyl-, trifluoromethanesulfonyl, and 4-*tert*-butylbenzenesulfonyl all proved inferior to the *N*-nonaflyl catalyst **4** with regard to enantioselectivity. With regard to the silane component, triethylsilyl was optimum with regard to yield and enantioselectivity with *tert*-butyldimethylsilyl a close second. Trimethylsilane worked well but the volatility of the product resulted in lower yields. Triphenylsilane and phenyldimethylsilane gave distinctly lower yields of product and also somewhat lower enantioselectivities. At higher reaction temperatures enantioselectivities were lower, as might have been anticipated. However, the yields of product were also lower. At 23 °C, for example, the reaction of **2**, Et_3SiH, and catalyst **4** gave **3** in 28% yield and 69% ee. Changing solvent from CH_2Cl_2 to pentane increases the enantioselectivity of the reaction **2**→**3**, but decreases the yield. Thus, we regard the conditions shown in Scheme 1 as close to optimal.

A number of other examples of enantioselective hydrosilylation of α'-diazo-α,β-enones using the catalyst **4** were studied leading to the following results. The optical rotations (OR) shown are at 23 °C for $c = 1$ in $CHCl_3$. The enantioselectivities were determined by HPLC analysis using chiral columns (Whelk 01, Chiralcel OD, or Chiralcel OJ). The absolute configurations of the α'-silylated-α,β-enones obtained by the use of catalyst **4** are based on the good enantioselectivity in each case, the analogy with **3** whose absolute configuration has been established, and the observation of strong dextrorotation in each case, which also leads to the stereochemistry shown by application of the octant rule.



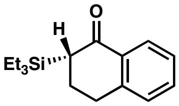
$R_3 = Et_3$, 83% ee, OR +75

R_3 = *t*-BuMe$_2$, 86% ee, OR +71



$R_3 = Et_3$, 77% ee, OR +170

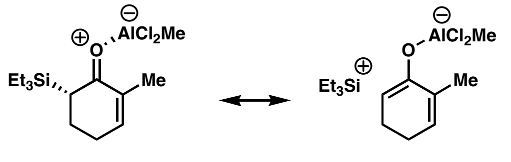
R_3 = *t*-BuMe$_2$, 80% ee, OR +181



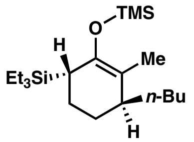
90% ee

With a serviceable method for the enantioselective synthesis of 6-triethylsilyl-2-methyl-2-cyclohexenone (**3**) we next evaluated this compound as a dienophile in Lewis acid-catalyzed Diels–Alder reactions. Measurements of infrared absorption using an internal IR probe (REACT-IR) in CH_2Cl_2 solution at −78 °C showed that the carbonyl stretching frequency of **3** at 1632 cm^{-1} was replaced by an absorption band at 1546 cm^{-1} when 1 equiv of $MeAlCl_2$ was added. Despite this indication of complexation there was very little reaction of the complex with 1,3-cyclopentadiene at −78 °C over the course of a few hours. Although this result is somewhat surprising since cyclopentadiene is one of the most reactive dienes, and methylaluminum dichloride is one of the most powerful catalytic Lewis acids, it can be understood as a consequence of the powerful electron-donating effect of the triethylsilyl group into the Lewis acid–carbonyl complex, as indicated below. It should be noted that there is a considerable measure of electron donation from the α-triethylsilyl group into the carbonyl group of **3** even without Lewis acid complexation, as is clear from the carbonyl stretching frequencies of **3** (1653 cm^{-1}) and 2-methyl-2-cyclohexenone (1676 cm^{-1}) (Δ 23 cm^{-1}). Since the strong electron donation by the triethylsilyl substituent diminishes the electrophilicity of C(β) of the α,β-enone, it can be expected to reduce Diels–Alder reactivity with a π-electron-rich diene such as cyclopentadiene. The Diels–Alder reaction did proceed to the extent of 50% conversion with $MeAlCl_2$ in CH_2Cl_2 at −20 °C after 12 h. Although the *endo*–*exo* selectivity was good (17:1), the facial selectivity for addition to the α,β-double bond of

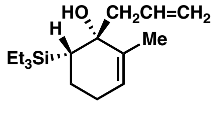
3 was only 3:1. The study of a few other dienes with **3** and MeAlCl$_2$ similarly showed only low selectivity of attack trans versus cis to the triethylsilyl group at C(6). Thus, it is clear that as a control element in Lewis acid-catalyzed Diels–Alder additions to 2-cyclohexenones a 5-trialkylsilyl group[1] is more effective than a 6-trialkylsilyl group.



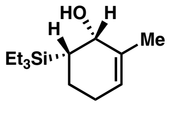
Nonetheless, the silyl group in **3** did direct other reactions to be highly diastereoselective. Thus, we have observed that **3** was converted efficiently into either **5** (conjugate addition of Bu$_2$CuLi and TMSCl in Et$_2$O at −78 °C; 100% yield and 15:1 diastereoselectivity), **6** (allylmagnesium chloride in ether at −78 °C; 100% yield and 14:1 diastereoselectivity), or **7** (diisobutylaluminum hydride in toluene; 93% yield and complete diastereoselectivity).



5



6



7

As a result of the studies reported herein, a short and effective process is available for the enantioselective synthesis of chiral α′-silylated-α,β-enones using a chiral Rh(II) catalyst. In addition, our results show that the electron releasing property of the trialkylsilyl group attenuates the reactivity of Lewis acid complexes of such α′-silylated-α,β-enones with π-electron-rich 1,3-dienes. In other reactions of the α′-silylated-α,β-enones the α′-silyl group can serve as an effective controller of diastereoselectivity. Research is underway to demonstrate significant applications of these findings.

References and notes

1. Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044–9045.
2. (a) Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 351–352; (b) Enders, D.; Lohray, B. B.; Burkamp, F.; Bhushan, V.; Hett, R. *Liebigs Ann.* **1996**, 189–200.
3. See also, Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 7–10.
4. Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741–1744.
5. (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964; (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1997**, *Coll. Vol. IX*, 197–202.
6. To a solution of rhodium catalyst **4** (131 mg, 0.073 mmol) in CH$_2$Cl$_2$ (70 mL) was added Et$_3$SiH (4.6 mL, 29.4 mmol) at −78 °C. A solution of **2** (1.53 g, 11.2 mmol) in CH$_2$Cl$_2$ (10 mL) was slowly added over 4 h. The reaction mixture was kept at −78 °C for 16 h before being slowly warmed up to 23 °C over 3 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (4% EtOAc/hexane) to give 1.7 g (70%) of the desired product (+)-**3** as a pale yellow liquid: R_f 0.55 (10% EtOAc/hexane); $[\alpha]_D^{23}$ +84.1 (c 1, CHCl$_3$); FTIR (film) 1652.8 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.63 (m, 1H), 2.34 (t, $J = 5$ Hz, 1H), 2.31–2.35 (m, 2H), 2.24–2.14 (m, 1H), 2.00–1.95 (m, 1H), 1.76 (d, $J = 2$ Hz, 3H), 0.94 (t, $J = 7.8$ Hz, 9H), 0.63 (q, $J = 7.8$ Hz, 6H) ppm; ^{13}C NMR (CDCl$_3$, 125 MHz) δ 201.5, 143.6, 136.5, 38.5, 25.7, 24.7, 16.9, 7.9, 3.9 ppm; HRMS (EI$^+$) m/z calcd for $[C_{13}H_{24}OSi]^+$: 224.1597, found: 224.1606; 94% ee, elution time $t_{major} = 7.71$ min; resolution of enantiomers of **3** was achieved by using an (S,S) Whelk 01 column, 2% i-PrOH in hexane as a eluent, a flow rate of 1 mL/min, detection wavelength of 225 nm with elution time $t_{fast} = 7.7$ min, $t_{slow} = 10.4$ min.