External Chiral Ligand-Mediated Enantioselective Peterson Reaction of α-Trimethylsilanylacetate with Substituted Cyclohexanones

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ABSTRACT



The asymmetric Peterson reaction of an α -trimethylsilanylacetate with 4-substituted and 3,5-disubstituted cyclohexanones was mediated by an external chiral tridentate ligand to give the corresponding olefins with an axial chirality in high yields and enantioselectivities of up to 85%.

The past two decades have witnessed considerable progress in the asymmetric Horner–Wadsworth–Emmons (HWE) and Wittig olefination reactions.¹ Since the first report by Tömösközi and Janzsó in 1962,² considerably energetic efforts have been devoted to establish the asymmetric HWE^{3,4} and Wittig⁵ reactions of chirally modified reagents. Some recent work has focused on enantioselectivity using chiral

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ligands in HWE⁶ and Wittig⁷ olefinations. However, little effort has been devoted to the asymmetric Peterson reaction except for Gais's chiral ester approach.⁸ The olefination reaction of an α -silanyl carbanion with a carbonyl compound has been widely utilized as a synthetic method for a variety of substituted olefins⁹ because of its advantages over Wittig-type reaction in the higher reactivity of α -silanyl carbanions than the corresponding phosphorus reagents and simpler workup and purification procedure from the absence of phosphorus side products. We now report the first example of the enantioselective Peterson olefination reaction of an α -silanyl ester enolate with substituted cyclohexanones by mediation of an external chiral ligand.

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As part of our studies aimed at chiral ligand-controlled asymmetric reactions¹⁰ we have already developed the asymmetric HWE reaction of a phosphonate **2a** with 4-*tert*-

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butylcyclohexanone **1a** under control of a chiral diether **5** giving the corresponding olefin **4a** (Y = 2-Naph, R¹ = *t*-Bu, R² = H) in 90% ee.^{6b} Extension of the procedure to a phosphonate **2b** possessing an ester portion, however, was unsatisfactory, giving **4b** (Y = CO₂Et, R¹ = *t*-Bu, R² = H) in 0% ee. On the basis of our previous finding that a reaction of a lithium ester enolate with an imine or aldehyde is controllable by **5**,¹¹ we chose an α -trimethylsilanyl ester **2c** as a silico equivalent to a phosphonate **2b**. A chelate of a lithium enolate of **2c** with **5** undergoes a face differentiating equatorial¹² attack to **1a**, giving **3** that instantly eliminates lithium trimethylsilanoxide in *syn* fashion to result in the formation of an axially chiral olefin **4c** (Y = CO₂R, R¹ = *t*-Bu, R² = H).

Successive treatment of $2c^{13}$ with LDA in the presence of 1.3 equiv of 5^{14} in toluene at -20 °C for 1 h to generate a lithium enolate-**5** chelate, and then with **1a** at -78 °C for 1 h directly gave an olefin *S*-(+)-**4c** (Y = 2,4-dimethyl-3-pentyloxycarbonyl, $R^1 = t$ -Bu, $R^2 = H$) in 83% yield. The enantioselectivity was determined to be 27% ee by chiral stationary phase HPLC (DAICEL Chiralcel OD-H, propan-2-ol/hexane 1/1000). The absolute configuration of (+)-**4c** was determined to be *S* by reduction with DIBALH in toluene to the corresponding (+)-allylic alcohol of the established absolute configuration.¹⁵

We then examined several factors to improve the enantioselectivity of the reaction. The size of the ester component of **2c** affected enantioselectivity, giving 19% and 23% ee with use of ethyl and *tert*-butyl esters, respectively. Another chiral ligand, sparteine **6**, was not satisfactory in the reaction of **2c** with **1a** to give *S*-(+)-**4c** in 14% ee. Fortunately a tridentate amino diether **7**¹⁶ gave *R*-(-)-**4c** in 52% ee of moderate selectivity.¹⁷ Another silyl group TBDMS, instead of TMS, at the α -position of the ester **2c** using **7** gave the olefin (-)-**4c** in 46% ee and 81% yield.

When the mixture of the lithium enolate of 2c and chiral ligand 7 was allowed to warm to 0 °C and stand at the same

temperature for 6 h to make sure the chelate formation before treatment with 1a, 4c was obtained in as high as 84% ee and 18% chemical yield. Since the Claisen-type condensation of the lithium enolate seemed one of the factors responsible for the low chemical yield and also for the improved enantioselectivity, the effect of the side products of the Claisen reaction, lithiated keto ester and lithium 2,4-dimethyl-3-pentoxide, on enantioselectivity were examined. The presence of 1 equiv of lithiated keto ester (2,4-dimethyl-3pentyl acetoacetate) was a moderate improving factor to afford (-)-4c in 61% ee in the reaction of 2c with 1a using 7 at -78 °C. The presence of 1 equiv of lithium 2,4dimethyl-3-pentoxide improved the enantioselectivity up to 65% from 52%. Other lithium alkoxides derived from ethanol, phenol, pentan-3-ol, and (-)- and (+)-menthol exhibited negative or marginal effects on enantioselectivity, giving (-)-4c in 44%, 29%, 54%, 50%, and 51% ee, respectively.

Since Claisen-type condensation consumes the lithium enolate of 2c, the increased ratio of chiral ligand 7 to the enolate seemed an improving factor of the enantioselectivity. In the presence of 12 equiv of 7 the reaction of 3 equiv of 2c with 1a at -78 °C afforded (-)-4c in 73% ee and 98% yield. The ligand 7 was recovered in quantitative yield and was recyclable. The reaction above at -100 °C for 0.5 h gave (-)-4c in 85% ee and 95% yield. On the contrary, the reaction using 1.5 equiv of the enolate and 6 equiv of 7 at -100 °C gave (-)-4c in 52% ee and 92% yield. The diminished enantioselectivity was probably due to the negative influence of lithium silanoxide, which is the side product in every Peterson reaction.

Therefore it was also a logical extension to examine the effect of lithium trimethylsilanoxide. Actually, the addition of the equimolar silanoxide to the enolate exhibited a negative effect to decrease the enantioselectivity down to 54% in the reaction of 3 equiv of **2c** with **1a** under 12 equiv of **7** at -100 °C. The use of 3 equiv of the lithium enolate – chiral ligand complex was effective in surmounting the negative influence of lithium silanoxide, because at least 2 equiv of the reagent complex are free from complexation with lithium silanoxide.

The enantioselective Peterson reactions of the lithium enolate of **2c** with 4-phenyl-, 4-methyl-, and 3,5-disubstituted¹⁸ cyclohexanones **1b**-**d** were examined under the established conditions and gave the corresponding chiral olefins **4d**-**f** in enantioselectivity of 76, 70, and 80%,¹⁹ respectively (Table 1).²⁰

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⁽¹⁷⁾ The use of lithium *N*-trityl-*tert*-butylamide (Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515–2518) instead of LDA gave **4c** in the same level of 50% ee.

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⁽²⁰⁾ A typical procedure (Table 1): A solution of **2c** (1.5 mmol) in toluene (2.5 mL) was added to a solution of LDA (1.6 mmol) in toluene (2.5 mL) at -78 °C. After the mixture was stirred at -78 °C for 0.5 h a solution of **7** (6.0 mmol) in toluene (1.5 mL) was added dropwise over 10 min. The mixture was stirred for 1 h at -20 °C, and allowed to cool to -100 °C. A solution of **1a** (0.5 mmol) in toluene (1.5 mL) was added dropwise over a period of 5 min, and the whole was stirred for 0.5 h at the same temperature and was then quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layers were washed with brine

Table 1.Asymmetric Peterson Olefination of 2c with 1Mediated by 7 and Conversion to 8

	-					
\mathbb{R}^1	\mathbb{R}^2	4	yield/%	ee/%	8	yield/%
t-Bu	Н	с	95	85 (<i>R</i>)	С	94
Ph	Н	d	95	76 (<i>R</i>)	d	99
Me	Н	е	95	70 (<i>R</i>)	е	95
Н	Me	f	99	80		

Since transfer of axial chirality to central chirality is a useful process, we examined the chirality transfer of **4**. Thus, treatment of R-(-)-**4c** of 45% ee with LDA in THF at 0 °C for 0.5 h gave, after workup with aqueous ammonium chloride, the endo-olefin R-(+)-**8c** ($[\alpha]^{25}_{\text{D}}$ +26.4 (*c* 1.06, CHCl₃)) in nearly quantitative yield (Table 1, Scheme 2).²¹



The enantiomeric excess of 8c was determined to be 46% by a chiral stationary phase HPLC (DAICEL Chiralcel OD-H, propan-2-ol/hexane 1/5000), indicating the stereoselective deprotonation of 4c and subsequent isomerization—proto-



nation taking place without any loss of enantiomeric purity. The absolute configuration of (+)-8c was determined to be *R* by the alternative chemical synthesis of S-(-)-8c: S-(-)-4-tert-butyltrimethylsilyloxycyclohexene of 86% ee, prepared under the established enantioselective deprotonation protocol with lithium (R,R)-bis $(\alpha$ -methylbenzyl)amide and in situ trap with trimethylchlorosilane,²² was converted to the corresponding triflate through lithiation with methyllithium and subsequent treatment with N-phthaloyltriflate.²³ The triflate was then coupled with bromozinc 2,4-dimethyl-3-pentyl acetate under bis(triphenylphosphine)-palladium catalysis²⁴ in THF at room temperature for 7 h to give S-(-)-8c ($[\alpha]^{25}$ _D -53.3 (c 0.97, CHCl₃)) of the defined absolute configuration in 71% yield. The allylic proton syn to an ester carbonyl group of 4c was deprotonated to fix the C-C double bond in accordance with precedents in stereoselective olefin formation.²⁵ The exo-olefins 4c-e with a 4-substituent were converted to the corresponding endo-olefins 8c-e in perfect stereoselectivity as shown in the Table 1.²⁶

In summary, the first chiral ligand-mediated asymmetric Peterson reaction of an α -trimethylsilanylacetate with substituted cyclohexanones was developed by using an external chiral tridentate amino diether. Suppression of the negative influence by lithium trimethylsilanoxide was key to the success in high enantioselectivity. Stereospecific transfer of an axial chirality to a central one was carried out by using LDA as a deprotonation agent.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for for **2c**, **4**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

and dried over sodium sulfate. Concentration and silica gel column chromatography (benzene/hexane 1/4) gave **4c** (143 mg, 95%) as a colorless oil of $[\alpha]^{25}_D - 43.4$ (*c* 0.99, EtOH). HPLC (DAICEL Chiralcel OD-H, propan-2-ol/hexane 1/1000, 0.3 mL/min, 254 nm) major 18.8 min, minor 14.4 min; 85% ee. ¹H NMR (500 MHz, CDCl₃) δ 0.86 (s, 9H), 0.87–0.91 (m, 12H), 1.08–1.29 (m, 3H), 1.80–1.95 (m, 5H), 2.14–2.34 (m, 2H), 3.85–3.88 (m, 1H), 4.62 (dd, J = 6.3, 6.3 Hz, 1H), 5.63 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 17.0, 19.3, 27.2, 28.2, 28.8, 29.3, 32.1, 37.5, 47.5, 81.1, 112.7, 162.5, 166.7. IR (neat) 1710, 1650 cm⁻¹. MS (EI) *m*/*z* 294 (M⁺), 196, 179. Anal. Calcd for C₁₉H₃₄O₂: C, 77.50; H, 11.64. Found: C, 77.29; H, 11.86.

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