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

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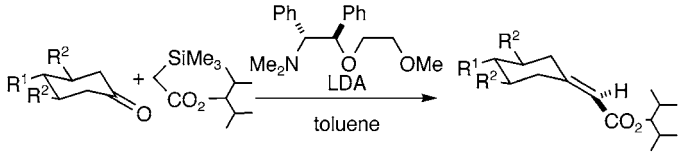
ABSTRACT



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 Wittig[5] reactions of chirally modified reagents. Some recent work has focused on enantioselectivity using chiral ligands in HWE[6] and Wittig[7] 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 olefins[9] 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.

As part of our studies aimed at chiral ligand-controlled asymmetric reactions[10] we have already developed the asymmetric HWE reaction of a phosphonate **2a** with 4-*tert*-

(1) Reviews: (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (b) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579−594.

(2) Tömösközi, I.; Janzsó, G. *Chem. Ind. (London)* **1962**, 2085−2086.

(3) Reactions of chiral phosphonates: (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754−5756. (b) Denmark, S. E.; Chen, C.-T. *Heteroat. Chem.* **1995**, *6*, 133−144. (c) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674−10676.

(4) Reactions of chiral phosphonates bearing an ester group at the α-position: (a) Gais, H.-J.; Schmiedl, G.; Ball, W. A.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773−1774. (b) Rehwinkel, H.; Skupsch, J.; Vorbrüggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775−1776. (c) Takahashi, T.; Matsui, M.; Maeno, N.; Koizumi, T. *Heterocycles* **1990**, *30*, 353−357. (d) Tanaka, K.; Ohta, Y.; Fuji, K.; Taga, T. *Tetrahedron Lett.* **1993**, *34*, 4071−4074. (e) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802−3804. (f) Denmark, S. E.; Rivera, I. *J. Org. Chem.* **1994**, *59*, 6887−6889. (g) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077−1080. (h) Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805−826.

(5) (a) Bestman, H. J.; Lienert, J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 763−764. (b) Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979−1982.

(6) (a) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753−755. (b) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 515−517. (c) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997−3000. (d) Sano, S. *Yakugaku Zasshi* **2000**, *120*, 432−444.

(7) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 3446−3447.

(8) Gais, H.-J.; Schmiedl, G.; Ossenkamp, R. K. L. *Liebigs Ann./Recl.* **1997**, 2419−2431.

(9) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784. (b) Review: Ager, D. J. *Org. React.* **1990**, *38*, 1−223.

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butylcyclohexanone **1a** under control of a chiral diether **5** giving the corresponding olefin **4a** (Y = 2-Naph, R^1 = *t*-Bu, R^2 = H) in 90% ee.[6b] Extension of the procedure to a phosphonate **2b** possessing an ester portion, however, was unsatisfactory, giving **4b** (Y = CO_2Et, R^1 = *t*-Bu, R^2 = 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 equatorial[12] 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 = CO_2R, R^1 = *t*-Bu, R^2 = 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-3-pentyl 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 2,4-dimethyl-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-disubstituted[18] 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]

(10) (a) Tomioka, K. *Synthesis* **1990**, 541−549. (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974−12975. (c) Fujihara, H.; Nagai K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (d) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932−8939.

(11) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. (b) Nomura, Y.; Iguchi, M.; Doi, H.; Tomioka, K. *Chem. Pharm. Bull.* **2002**, *50*, 1131−1134.

(12) (a) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546. (b) Gillies, M. B.; Tønder, J. E.; Tanner, D.; Norrby P.-O. *J. Org. Chem.* **2002**, *67*, 7378−7388.

(13) The α-trimethylsilanylacetate **2c** was prepared in 74% yield upon treatment of 2,4-dimethyl-3-pentyl acetate with lithium cyclohexylisopropylamide and silylation with trimethylchlorosilane. Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67−72.

(14) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266−8268. Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351−9357.

(15) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 3252−3264.

(16) (a) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141−2144. (b) Kambara, T.; Tomioka. K. *J. Org. Chem.* **1999**, *64*, 9282−9285. (c) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715−716.

(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.

(18) Majewski, M.; Gleave, D. M. *J. Org. Chem.* **1992**, *57*, 3599−3605.

(19) The enantiomeric excess of **4f** was determined by a chiral stationary phase HPLC (DAICEL Chiralcel OD-H, propan-2-ol/hexane 1/100) of the corresponding allylic alcohol, which was prepared by reducing **4f** with DIBALH.

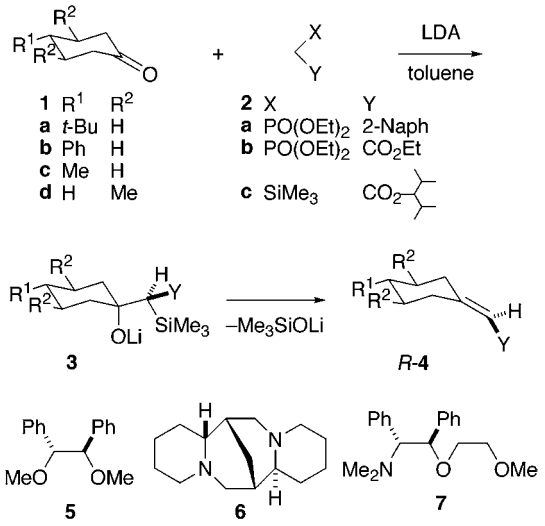
(20) A typical procedure (Table 1): A solution of **2c** (1.5 mmol) in toluene (2.5 mL) was added to a solution of LDA (1.6 mmol) in toluene (2.5 mL) at −78 °C. After the mixture was stirred at −78 °C for 0.5 h a solution of **7** (6.0 mmol) in toluene (1.5 mL) was added dropwise over 10 min. The mixture 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 **1** Mediated by **7** and Conversion to **8**

R^1	R^2	**4**	yield/%	ee/%	**8**	yield/%
t-Bu	H	**c**	95	85 (*R*)	**c**	94
Ph	H	**d**	95	76 (*R*)	**d**	99
Me	H	**e**	95	70 (*R*)	**e**	95
H	Me	**f**	99	80		

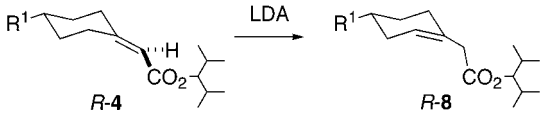
Since transfer of axial chirality to central chirality is a useful process, we examined the chirality transfer of **4**. Thus, treatment of *R*-(−)-**4c** of 45% ee with LDA in THF at 0 °C for 0.5 h gave, after workup with aqueous ammonium chloride, the endo-olefin *R*-(+)-**8c** ($[\alpha]^{25}_D$ +26.4 (*c* 1.06, $CHCl_3$)) in nearly quantitative yield (Table 1, Scheme 2).[21]

Scheme 1. Asymmetric Reaction of **2** with **1**



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-

Scheme 2. Conversion of *R*-**4** to *R*-**8** by Isomerization



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(α-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 catalysis[24] in THF at room temperature for 7 h to give *S*-(−)-**8c** ($[\alpha]^{25}_D$ −53.3 (*c* 0.97, $CHCl_3$)) 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.

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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. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.29; H, 11.86.

(21) Chirality transfer of **4c** (Y = CO_2H, R^1 = *t*-Bu, R^2 = H) to **8** has been described without any comment on stereochemistry. Duhamel, L.; Ravard, A.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **1990**, *1*, 347−350.

(22) (a) Cousins, R. P. C.; Simpkins, N. S. *Tetrahedron Lett.* **1989**, *30*, 7241−7244. (b) Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994−996.

(23) Nozawa, D.; Takikawa, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2043−2046.

(24) Orsini, F.; Pelizzoni, F. *Synth. Commun.* **1987**, *17*, 1389−1402.

(25) (a) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333−1336. (b) Galatsis, P.; Manwell, J. J.; Millan, S. D. *Tetrahedron Lett.* **1996**, *37*, 5261−5264.

(26) *S*-**4d**,**e** of 14% ee and 24% ee were converted to *S*-**8d**,**e** of 15% ee and 25% ee, respectively.