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A novel method for the preparation of benzylidenecyclohexanes with high optical purity

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Abstract—The enantioselective reaction of the α-thio carbanion derived from 1-phenyl-1-(phenylthio)-1-(tributylstannyl)methane with 4-substituted cyclohexanones in the presence of bis(oxazoline)s gave the products as a diastereomeric mixture. Each diastereomer obtained had high optical purity. The reaction of the α-seleno carbanion derived from the bis(phenylseleno)acetal also showed high enantioselectivity. The stereospecific elimination of the isolated diastereomers on treatment with methanesulfonyl chloride and triethylamine afforded axially chiral benzylidenecyclohexanes with high enantioselectivities up to 99% ee.

The axially chiral cyclohexylidene compound was first recognized in 1910 by the optical resolution with brucine.[1] Recently, the unique chiroptical property of axially chiral alkylidenecyclohexanes has been studied.[2] Stereoselective syntheses of axially chiral olefins hitherto known are based on diastereoselective reactions using various chiral auxiliaries,[3,4] some of them showing high diastereoselectivity. For enantioselective reactions, oxidation of β-seleno ketones into optically active cyclohexylidene ketones[5] and dehydrohalogenation with chiral metal alkoxides or amides[6] have been reported. Very recently, enantioselective versions of the Peterson olefination[7] and the Horner–Wadsworth–Emmons[8,9] reaction have been reported showing good to moderate selectivities; one version achieved 90% ee of the product in the reaction of 4-*tert*-butylcyclohexanone with lithium phosphonate in the presence of a chiral ligand.[8b] Although such stereoselective reactions are known, it has been still desired to develop a more efficient reaction for the preparation of enantiomerically pure axially chiral olefins. We have previously reported highly enantioselective lithiation–substitution reactions in the presence of bis(oxazoline)s involving an asymmetric replacement of prochiral hydrogens adjacent to sulfur.[10,11] We now report the first synthetic method for enantiomerically pure axially chiral benzylidenecyclohexanes including the enantioselective reaction of cyclohexanones with the α-thio and α-seleno carbanions and subsequent stereospecific formation of a double bond.

The α-carbanion of benzyl phenyl sulfide was prepared on treatment of 1-phenyl-1-(phenylthio)-1-(tributylstannyl)methane **1a** with *n*-BuLi and a chiral ligand.[10b] Reaction of the sulfide **1a** with 1.15 equiv of *n*-BuLi and 1.2 equiv of a chiral ligand in cumene for 10 min at −78 °C formed Li-**1a**, which was then reacted with 4-substituted cyclohexanones (1.3 equiv) to give the products **4**–**6**.[12] The yields and the enantiomeric excesses obtained in the reactions with 4-*tert*-butyl-, 4-methyl-, and 4-phenylcyclohexanones using various chiral ligands are shown in Table 1.[13] The reaction of Li-**1a** with 4-*tert*-butylcyclohexanone in the presence of (−)-sparteine gave the product **4** with good diastereoselectivity but with low enantioselectivity (entry 1). On the other hand, the reaction using bis(oxazoline)-^{i}Pr **3a** as a chiral ligand afforded the product **4** with excellent enantioselectivity (99% ee for the *cis* isomer, 99% ee for the *trans* isomer, entry 2). Each diastereomer was easily separated by column chromatography. Bis(oxazoline)-^{i}Pr **3a** showed higher enantioselectivity than other bis(oxazoline)s **3b** and **3c** (entries 3 and 4). The reaction of Li-**1a** with 4-methyl- and 4-phenylcyclohexanones in the presence of bis(oxazoline)-^{i}Pr **3a** also afforded the products **5** and **6** with high enantioselectivity (entries 5 and 6). We next examined the enantioselective reaction of the α-seleno carbanion generated by treatment of 1,1′-bis(phenylseleno)-1-phenylmethane **1b** with *n*-BuLi in

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Keywords: Asymmetric synthesis; Carbanion; Enantioselective substitution; Chiral olefin.

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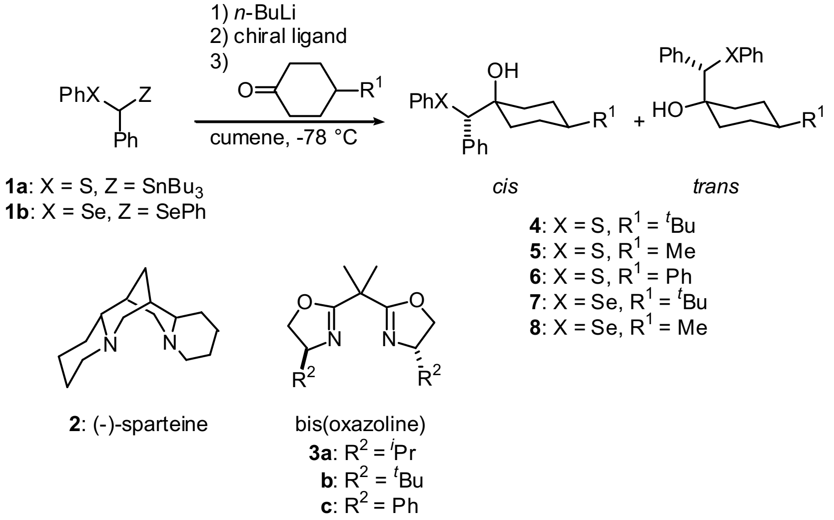
Table 1. Enantioselective reaction of lithiated **1** with 4-substituted cyclohexanones



Entry	Substrate	Ligand	Electrophile R^1	Product	Yield (%)	Ratio[a]	Ee (%)[b]	
						cis:*trans*	*cis*	*trans*
1	**1a**	**2**	^{t}Bu	**4**	71	74:26	8	0
2[c]	**1a**	**3a**	^{t}Bu	**4**	65	63:37	99	99
3	**1a**	**3b**	^{t}Bu	**4**	68	64:36	92	95
4	**1a**	**3c**	^{t}Bu	**4**	43	76:24	52	32
5	**1a**	**3a**	Me	**5**	71	65:35	99	99
6[c]	**1a**	**3a**	Ph	**6**	53	52:48	99	99
7[d]	**1b**	**3b**	^{t}Bu	**7**	61	65:35	86	90
8[d]	**1b**	**3b**	Me	**8**	73	70:30	89	90

[a] The diastereomer ratio was determined by ^{1}H NMR analysis.

[b] The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H (entries 1–4, 6, and 7), Daicel Chiralcel OD-H (entries 5 and 8), and Daicel Chiralcel OJ-H (entry 5).

[c] The reaction was carried out at −90 °C.

[d] *n*-BuLi (1.3 equiv), **3b** (1.4 equiv), and 4-methylcyclohexanone (2.0 equiv) were used.

the presence of bis(oxazoline) **3a** or **3b**. There are a few preceding reports of reactions of α-seleno carbanions, which show a good level of enantioselectivity.[14,15] The enantioselective reaction of the α-seleno carbanion with 4-*tert*-butyl- or 4-methylcyclohaxanone in the presence of bis(oxazoline)-^{i}Pr **3a** showed high enantioselectivity (entries 7 and 8),[16] which was the highest ever reported in reactions using α-seleno carbanions.[17]

The obtained products **4**–**8** were converted to chiral benzylidenecyclohexanes by the modified reaction reported in the literature,[18,19] in which α-arylthio- or α-arylseleno-β-hydroxy compounds can be transformed to alkenes through the stereospecific *anti*-elimination of the arylthio or the arylseleno group together with the methanesulfonyloxy group. Thus, the separated diastereomeric alcohols **4**–**8** were reacted with methanesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature to give the axially chiral benzylidenecyclohexanes **9**–**11** (Table 2).[20] Optical purity of **9**–**11** was determined by HPLC analyses using Chiralcel OD-H. No loss of optical purity was observed during the β-elimination. The β-elimination proceeded in an *anti* fashion to give **9**–**11** stereospecifically. Especially, enantiomerically pure *cis*-sulfides *cis*-**4**–**6** gave (*M*)-benzylidenecyclohexanes (*M*)-**9**–**11** and *trans*-sulfides *trans*-**4**–**6** afforded (*P*)-**9**–**11**. Thus, both enantiomers were obtained in highly optically active forms. This procedure is the first example for the preparation of enantiomerically pure chiral benzylidenecyclohexanes from the corresponding cyclohexanones through an enantioselective reaction and the subsequent *anti*-elimination. The absolute stereochemistry of **9**–**11** was assigned by comparison of the values of the specific rotation with those reported.[3c,d]

In summary, we have demonstrated the first highly enantioselective preparation of axially chiral benzylidenecyclohexanes through an enantioselective reaction of α-thio- and α-seleno carbanions of benzyl phenyl sulfide and benzyl phenyl selenide in the presence of bis(oxazoline)s and subsequent stereospecific elimination.

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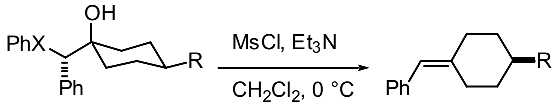
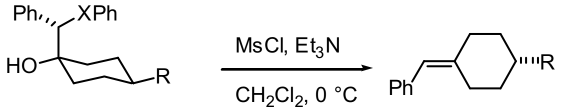
Table 2. Preparation of axially chiral benzylidenecyclohexanes **9**–**11** from *cis*- and *trans*-**4**–**8**



cis-**4**: X = S, R = ^{t}Bu
cis-**5**: X = S, R = Me
cis-**6**: X = S, R = Ph
cis-**7**: X = Se, R = ^{t}Bu
cis-**8**: X = Se, R = Me

(*M*)-**9**-**11**



trans-**4**: X = S, R = ^{t}Bu
trans-**5**: X = S, R = Me
trans-**6**: X = S, R = Ph
trans-**7**: X = Se, R = ^{t}Bu
trans-**8**: X = Se, R = Me

(*P*)-**9**-**11**

Entry	Substrate		Product	Yield (%)	Ee (%)[a]	Config.
		Ee (%)				
1	*cis*-**4**	99	**9**	51	99	(*M*)
2	*cis*-**5**	99	**10**	64	99	(*M*)
3	*cis*-**6**	99	**11**	57	99	(*M*)
4	*cis*-**7**	86	**9**	88	86	(*M*)
5	*cis*-**8**	89	**10**	80	89	(*M*)
6	*trans*-**4**	99	**9**	55	99	(*P*)
7	*trans*-**5**	99	**10**	50	99	(*P*)
8	*trans*-**6**	99	**11**	52	99	(*P*)
9	*trans*-**7**	90	**9**	89	90	(*P*)
10	*trans*-**8**	90	**10**	90	90	(*P*)

[a] The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD-H.

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12. When the reaction was carried out in a coordinative solvent such as THF or Et_2O, **1a** could be lithiated on treatment with *n*-BuLi without addition of a chiral ligand, giving **4** in high yield but with low enantioselectivity after addition of **3a** and 4-*tert*-butylcyclohexanone.
13. Representative procedure: To a solution of **1a** (46.4 mg, 0.0948 mmol) in cumene (0.4 mL) was added *n*-BuLi (0.109 mmol) at −78 °C under argon and the solution was stirred for 10 min. Then a solution of **3a** (30.1 mg, 0.114 mmol) in cumene (0.3 mL) was added and the solution was stirred for 1 h. The reaction mixture was cooled to −90 °C and was added dropwise a solution of 4-*tert*-butylcyclohexanone (19.0 mg, 0.123 mmol) in cumene (0.3 mL). The solution was stirred for 1 h at this temperature and then saturated aqueous NH_4Cl was added. The aqueous layer was extracted with diethyl ether and combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate 97:3), giving *cis*-**4** (13.7 mg, 41%), and *trans*-**4** (8.2 mg, 24%). The diastereomer ratio was determined by ^1H NMR spectral analysis of the crude product. *cis*-**4**: R_f 0.34 (hexane/ethyl acetate 90:10); mp 93–94 °C; $[\alpha]_D^{25}$ +192.0° (*c* 1.41, $CHCl_3$); ^1H NMR δ 0.82 (s, 9H), 1.25–1.58 (m, 8H), 1.95–2.15 (m, 2H), 4.13 (s, 1H), 7.11–7.40 (m, 10H); HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH 95/5, 0.5 mL/min) t_R 16.4 [(*R*)], and 23.9 [(*S*), 99% ee] min. *trans*-**4**: R_f 0.23 (hexane/ethyl acetate 90:10); $[\alpha]_D^{25}$ +186.4° (*c* 1.15, $CHCl_3$); ^1H NMR δ 0.86 (s, 9H), 1.11–1.80 (m, 8H), 2.05 (m, 1H), 2.67–2.73 (m, 1H), 4.42 (s, 1H), 7.11–7.38 (m, 10H); HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH 95/5, 0.5 mL/min) t_R 16.9 [(*R*)], and 19.0 [(*S*), 99% ee] min.
14. (a) A good level of enantioselectivity has been reported in the reaction of non-dipole-stabilized α-seleno carbanions through a dynamic thermodynamic resolution pathway, see: Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409–1411; (b) Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721–1726; (c) Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694–700.
15. We have demonstrated that the enantioselective reaction of the α-thio carbanion derived from benzyl phenyl sulfide proceeds through a dynamic kinetic resolution pathway; see Ref. 10. The reaction of the α-seleno carbanion derived from benzyl phenyl selenide was confirmed to proceed through a dynamic thermodynamic resolution pathway, showing that the α-seleno carbanion is configurationally more stable than the α-thio carbanion. The results will be published in due course.
16. The reaction of **1b** taking a longer time for lithiation resulted in lower yield of the product.
17. We also examined the enantioselective reaction of 2-pyridyl selenide with 4-substituted cyclohexanone, but the obtained diastereomeric mixture could not be separated by column chromatography.
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20. Representative procedure: To a solution of *cis*-**4** (11.1 mg, 0.0313 mmol) in CH_2Cl_2 was added methanesulfonyl chloride (0.050 mL, 0.626 mmol) at 0 °C and the solution was stirred for 30 min. Triethylamine (0.22 mL, 1.57 mmol) was then added and the reaction mixture was stirred for 1 h. The cooling bath was removed and the mixture was stirred for an additional 1 h at room temperature. Usual work-up afforded an oil, which was purified by silica gel column chromatography (hexane), giving (*M*)-**9** (3.6 mg, 51%): $[\alpha]_D^{25}$ −43.0° (*c* 0.70, CH_3OH) [lit.[3c] −43.25 (*c* 1.23, CH_3OH)]; HPLC (Daicel Chiralcel OD-H, hexane, 0.2 mL/min) t_R 28.7 [(*M*)-**9**, 99% ee], and 33.4 [(*P*)-**9**] min.