Asymmetric Selenoxide Elimination Leading to Chiral Alkyl and Aryl Cyclohexylidenemethyl Ketones

Naoki Komatsu, Shuji Matsunaga, Toshio Sugita, and
Sakae Uemura*

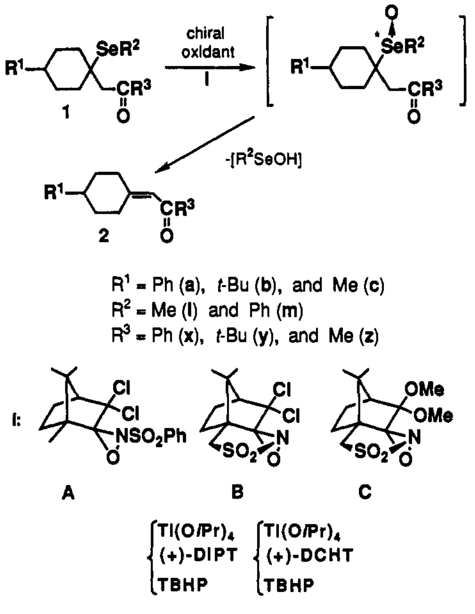
Division of Energy and Hydrocarbon Chemistry
Graduate School of Engineering, Kyoto University
Sakyo-ku, Kyoto 606-01, Japan

Received March 26, 1993

Asymmetric induction using organoselenium compounds is of current interest and presents a new trend in the field of organoselenium chemistry.[1] Although there have been many reports on the isolation of chiral stable selenoxides, the application of the chiral selenoxides to asymmetric induction is, as yet, limited to the following two types of reactions (five examples, to the best of our knowledge): (1) an asymmetric [2,3] sigmatropic rearrangement leading to chiral allylic alcohols (four examples)[2] and (2) an asymmetric selenoxide elimination leading to chiral allenic sulfones (only one example).[3] During the search for other applications of the asymmetric selenoxide elimination, we succeeded in a facile preparation of axially chiral alkyl and aryl cyclohexylidenemethyl ketones in high enantiomeric excess (up to 83% ee) and in excellent chemical yield. It is disclosed here that the recently developed Davis oxidant (**A**)[4] is strikingly useful for this asymmetric induction.

Chiral cyclohexylidene compounds have attractive chiroptical properties,[5] and their highly stereoselective preparation has been reported.[5-8] Thus, various benzylidenecyclohexane or alkylidenecyclohexane derivatives were synthesized with high stereoselectivity using chiral Wittig reagents.[6] For chiral cyclohexylidenemethyl carbonyl compounds, the carboxylic acid derivatives were prepared either by optical resolution[5b] or by asymmetric dehydrohalogenation with chiral lithium amides,[7] while the ketone, ester, and aldehyde derivatives were mainly derived from the chiral carboxylic acids thus prepared.[5a,d,8] The synthesis of chiral ketone derivatives from cyclohexylideneacetic acids was difficult because isomerization to the thermodynamically more stable endo olefins occurred, as previously reported by Walborsky.[5a] We also experienced such difficulties in the preparation of authentic samples. Therefore, we decided to take a new approach for these chiral ketones, using asymmetric selenoxide elimination, the successful results of which are reported here.

Scheme I[a]



R^1 = Ph (**a**), *t*-Bu (**b**), and Me (**c**)
R^2 = Me (**l**) and Ph (**m**)
R^3 = Ph (**x**), *t*-Bu (**y**), and Me (**z**)

[a] DIPT, diisopropyl tartrate; DCHT, dicyclohexyl tartrate; TBHP, *tert*-butyl hydroperoxide.

The starting cyclohexyl selenides **1** were prepared by treatment of the corresponding cyclohexanone selenoketals[9] with enol silyl ethers according to the literature method.[10] In all cases the selenides consisted of a single isomer, as confirmed by ^{1}H NMR spectral analysis. They were expected to have the *Z* configuration, because the Lewis acid catalyzed alkylation of conformationally rigid 4-*tert*-butylcyclohexanone selenoketals was known to occur stereoselectively from an equatorial face.[11] When the selenides were oxidized with either Davis oxidants (**A**,[4] **B**,[12] and **C**[13]) or Sharpless oxidants[14] (**D** and **E**), the corresponding axially chiral alkyl and aryl 4-substituted cyclohexylidenemethyl ketones **2** were obtained (Table I, Scheme I).[15]

As shown in Table I, the R^2 group had two marked effects upon this reaction: the use of a methyl moiety (**l**) instead of a phenyl moiety (**m**) increased the ee value dramatically and also accelerated the reaction. The former effect may be due to the steric difference between the two groups bonded to the selenium atom of the substrate; the large steric difference between the methyl moiety and the substituent-bearing cyclohexyl moiety led to the formation of a more stereoselective chiral selenoxide

---

(1) For reviews: (a) Kamigata, N.; Shimizu, T. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1991; Vol. 4, p 226. (b) Tomoda, S.; Usuki, Y.; Fujita, K.; Iwaoka, M. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1991; Vol. 4, p 249.

(2) (a) Davis, F. A.; Reddy, R. T. *J. Org. Chem.* **1992,** *57,* 2599. (b) Davis, F. A.; Stringer, O. D.; McCauley, J. P. *Tetrahedron* **1985,** *41,* 4747. (c) Reich, H. J.; Yelm, K. E. *J. Org. Chem.* **1991,** *56,* 5672. (d) Komatsu, N.; Nishibayashi, Y.; Uemura, S. *Tetrahedron Lett.* **1993,** *34,* 2339.

(3) (a) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1992,** 46. (b) Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *J. Org. Chem.*, in press.

(4) (a) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992,** *114,* 1428. (b) Davis, F. A.; Reddy, R. T.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989,** *111,* 5964.

(5) (a) Reddy, S. M.; Duraisamy, M.; Walborsky, H. M. *J. Org. Chem.* **1986,** *51,* 2361. (b) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1983,** *105,* 3252; (c) **1983,** *105,* 3264. (d) Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982,** *1,* 667. (e) Brewster, J. H.; Privett, J. E. *J. Am. Chem. Soc.* **1966,** *88,* 1419.

(6) (a) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992,** *114,* 10674. (b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992,** *33,* 7655. (c) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984,** *106,* 5754.

(7) (a) Vadecard, J.; Plaquevent, J.-C.; Duhamel, L.; Duhamel, P. *J. Chem. Soc., Chem. Commun.* **1993,** 116. (b) Duhamel, L.; Ravard, A.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **1990,** *1,* 347. (c) Duhamel, L.; Ravard, A.; Plaquevent, J.-C.; Davoust, D. *Tetrahedron Lett.* **1987,** *28,* 5517.

(8) The other reported procedure to obtain 4-substituted cyclohexylidene esters is *via* chiral sulfoxides prepared by Andersen synthesis, see: Solladie, G.; Zimmermann, R.; Bartsch, R.; Walborsky, H. M. *Synthesis* **1985,** 662.

(9) Clarembeau, M.; Cravador, A.; Dumont, W.; Hevesi, L.; Krief, A.; Lucchetti, J.; Ende, D. V. *Tetrahedron* **1985,** *41,* 4793.

(10) Nsunda, K. M.; Hevesi, L. *Tetrahedron Lett.* **1984,** *25,* 4441.

(11) (a) Krief, A.; Badaoni, E.; Dumont, W.; Hevesi, L.; Hermans, B.; Dieden, R. *Tetrahedron Lett.* **1991,** *32,* 3231. (b) Nakamura, E.; Horiguchi, Y.; Shimada, J.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983,** 796. (c) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980,** *21,* 71.

(12) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990,** *55,* 3715.

(13) Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991,** *56,* 1143.

(14) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980,** *102,* 5976. (b) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1984,** *63,* 66.

(15) A typical experimental procedure using Davis oxidant is as follows. Precooled (−20 °C) dry chloroform (2 mL) was added to a mixture of the selenide **1blx** (0.10 mmol, see Scheme I), Davis oxidant **A** (0.11 mmol), and several pieces of molecular sieves (4 Å, pellet) at −20 °C under an argon atmosphere. The mixture was stirred for 4 h at −20 °C and then directly submitted to preparative TLC (ethyl acetate/hexane = 1/19 as eluent) to afford (4-*tert*-butylcyclohexylidene)acetophenone (**2bx**) of 83% ee in 96% chemical yield. The ee value of the product was determined by HPLC using a Daicel Chiralcel OF column, and configuration of the product was determined to be *R* by the chemical correlation to the compounds derived from (*aR*)-(−)-(4-*tert*-butylcyclohexylidene)acetic acid of known configuration.

0002-7863/93/1515-5847$04.00/0

Table I. Synthesis of Chiral Cyclohexylidenemethyl Ketones **2** *via Asymmetric* Selenoxide Elimination[a]

	substrate (**1**)					conditions				
run	R^1	R^2	R^3	oxidant	solvent	time/h	(t/°C)	yield[b] (%)	ee[c] (%)	config[d]
1	**a**	**l**	**x**	**A**	CH_2Cl_2	3.5	–20	92	74	*R*[e]
2	**b**	**l**	**x**	**A**	$CHCl_3$[f]	4	–20	96	83	*R*
3	**b**	**l**	**x**	**A**	CCl_4	4	–20	100	82	*R*
4	**b**	**l**	**x**	**A**	CH_2Cl_2[f]	4	–20	92	81	*R*
5	**b**	**l**	**x**	**A**	$CHCl_3$[f]	0.5	*m*	89	75	*R*
6	**b**	**l**	**x**	**A**	$CHCl_3$[f]	2	0	72	79	*R*
7	**b**	**l**	**x**	**A**	CH_2Cl_2[f]	6.5	–78	100	49	*R*
8[g]	**b**	**l**	**x**	**A**	CH_2Cl_2[h]	4	–20	95	82	*R*
9[g]	**b**	**l**	**x**	**A**	methanol[i]	4	–20	96	81	*R*
10	**b**	**l**	**x**	**B**	CCl_4	4	–20	56	24	*S*
11	**b**	**l**	**x**	**C**	CCl_4	4	–20	95	6	*R*
12	**b**	**l**	**x**	**D**	CH_2Cl_2[f]	4	–20	100	2	*S*
13	**b**	**l**	**y**	**A**	$CHCl_3$[f]	5	–20	70	82	*R*
14	**b**	**l**	**z**	**A**	$CHCl_3$[f]	5	–20	97[j]	74	*R*
15	**b**	**m**	**x**	**A**	CH_2Cl_2	72	–20	66[k]	7	*R*
16	**b**	**m**	**x**	**D**	CH_2Cl_2	72	–20	64[k]	0	
17	**b**	**m**	**x**	**E**	CH_2Cl_2	72	–20	71[k]	1	*S*
18	**c**	**l**	**x**	**A**	CH_2Cl_2	4	–20	91	81	*R*[l]

[a] All the reactions were carried out in the presence of molecular sieves (4 Å, pellet). [b] Isolated yield. [c] Determined by HPLC on a Daicel Chiralcel OF or OJ column. [d] Determined by the authentic sample prepared by the reported methods (see supplementary material). [e] An authentic sample for **2ax** was not yet available, but *R*-configuration is highly expected from the optical rotation and the order of elution on HPLC. [f] The solvent was treated with anhydrous K_2CO_3 prior to use.[3a] [g] In the absence of molecular sieves. [h] Reagent grade CH_2Cl_2 was used under aerial conditions. [i] Aqueous HCl (1.0×10^{-3} mL, 1 N) was added. [j] Racemic compound **2bz** was reported in ref 17. [k] Estimated by ^1H NMR from the products contaminated with the starting substrate. [l] Reference 5a. [m] Room temperature.

intermediate. Such phenomena have also been observed in the asymmetric oxidation of sulfides to sulfoxides.[4] The rate acceleration effect may be due to the lower steric hindrance of the methyl (**l**) than the phenyl (**m**) moiety around the selenium atom, which is attacked by a sterically large oxidant. When a methyl moiety (**l**) in R^2 and Davis oxidant **A** were employed, high enantioselectivities (~74–83% ee) were obtained irrespective of the nature of R^1 and R^3. These results indicate that the method may be applicable generally to the synthesis of a wide range of cyclohexylidenemethyl ketones.

The oxidants also had a remarkable effect upon the ee value: Davis oxidant **A** gave the best result within our attempted experiments, while Davis oxidants **B** and **C** as well as Sharpless oxidants **D** and **E** were not effective. These results were in sharp contrast to asymmetric selenoxide elimination leading to chiral allenic sulfones,[3] where Sharpless oxidants were more effective than Davis oxidants. The chiral selenoxide, the key intermediate in this asymmetric induction, is known to racemize easily even with a small amount of water,[1a,2b] and the rate of racemization is much accelerated under the acidic conditions.[1a,2b,16] Our results indicate that the titanium complex of Sharpless oxidant promotes the racemization of the chiral selenoxide intermediate as a Lewis acid catalyst, while the racemization in the case of Davis oxidant, which is aprotic in nature,[4b] is slow. Thus, with Davis oxidant the chiral selenoxide may be eliminated before racemization occurs, while with Sharpless oxidant the chiral selenoxide loses its chirality by racemization before elimination, leading to an almost racemic product. Further, the fact that a similar selectivity was obtained by the use of methanol containing aqueous HCl as solvent suggested a very large rate of elimination. This enables us to develop an experimental procedure using reagent grade CH_2Cl_2 under aerial conditions. Further studies including mechanistic consideration will be reported in due course.

Acknowledgment. The present work was supported in part by a Grant-in-Aid for Scientific Research (No. 04453086) from the Ministry of Education, Science and Culture, Japan. Thanks are due to Mr. Yasuhiro Haseba for some experimental assistance.

Supplementary Material Available: Characterization data for new compounds and experimental details including the chemical correlation of the product **2** to authentic samples (7 pages). Ordering information is given on any current masthead page.

---

(16) Shimizu, T.; Kobayashi, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3761.

(17) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128.