

γ-Cyclodextrin-Bicapped C_{60}-Mediated Asymmetric Reduction of Ketones with $NaBH_4$

Takahiro Nishimura, Mitsuru Nakajima, Yasunari Maeda, Sakae Uemura,* Shin-ichi Takekuma[1], Hideko Takekuma,[1] and Zen-ichi Yoshida*,[1]

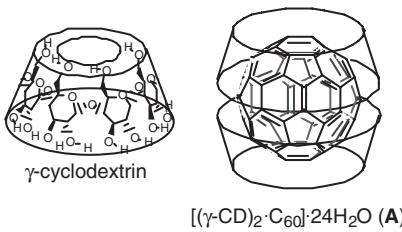
Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510

[1]Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University, 3-4-1, Kowakae, Higashi-Osaka-shi, Osaka 577-8502

Received April 21, 2004; E-mail: uemura@scl.kyoto-u.ac.jp

A supramolecular γ-cyclodextrin-bicapped C_{60}-mediated asymmetric reduction of prochiral alkyl aryl ketones using $NaBH_4$ as a reducing reagent affords chiral *sec*-alcohols with moderate enantioselectivity.

Supramolecular fullerene chemistry has been developing in recent years. The inclusion complexation of C_{60} by macrocyclic host molecules (host–guest chemistry) as well as the covalent fullerene functionalization in order to increase the solubility of C_{60} in organic solvent or water have been recognized as special topics in C_{60} chemistry. By these techniques the applications of utilizing the unique properties of C_{60} to materials and biological substrates have been much spread.[1] In our basic studies on the complexation of C_{60} with γ-cyclodextrin (γ-CD),[2,3] a method for a selective and high yield formation of the supramolecular inclusion complex of C_{60} with γ-CD (γ-cyclodextrin-bicapped C_{60} $[(\gamma\text{-CD})_2 \cdot C_{60}] \cdot 24H_2O$ (**A**), Fig. 1) has been found. We have also demonstrated a highly selective generation of stable C_{60}^{1-} and C_{60}^{2-} in DMSO (dimethyl sulfoxide) from **A** using NaH or $NaBH_4$ as a reducing reagent.[4] A generated C_{60} anion is expected to work as an electron mediator to cleave covalent bonds by the electron transfer reaction.[5] Supramolecular C_{60} complex **A** has a unique structure with a hydrophobic pocket around the belt region, where a chiral environment derived from successive chiral secondary hydroxy groups of γ-CD is present. If such a chiral environment could be used as a reaction site, enzyme-mimic asymmetric reaction could be realized to open the new world of the supramolecular catalysis. During our efforts to find the new function of **A** in organic reactions, C_{60}^{2-} species generated from **A** by the reaction with $NaBH_4$ in DMSO was found to promote the reduction of a variety of ketones to the corresponding alcohols under mild conditions and, interestingly, asymmetric induction occurred. We wish to report here the results of the supramolecular C_{60} (**A**)-mediated asymmetric reduction of prochiral ketones (Scheme 1).



$[(\gamma\text{-CD})_2 \cdot C_{60}] \cdot 24H_2O$ (**A**)

Fig. 1. γ-Cyclodextrin-bicapped C_{60} (bounded water molecules are omitted for clarity).

Results and Discussion

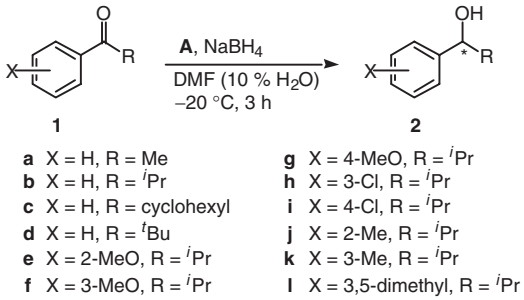
Acetophenone (**1a**) was chosen first as a substrate for this asymmetric reduction using $NaBH_4$ as a reducing reagent, because the selective formation of C_{60}^{2-} and the immediate decrease of such characteristic bands (950, 835 nm) after the addition of **1a** have been observed in our previous studies. Results of the reduction of **1a** in the presence of **A** under several conditions are listed in Table 1. Treatment of **1a** with $NaBH_4$ (1 equiv) in DMSO containing 10% H_2O in the presence of **A** (1 equiv) at 0 °C for 1 h under N_2 atmosphere afforded **2a** in 66% yield with 18% ee (Table 1, Entry 1).[6] The increase of the amount of $NaBH_4$ improved the product yield without any improvement of the ee value (Entries 2 and 3). The reaction in water was slow and gave a low ee value. When DMF (*N*,*N*-dimethylformamide) was used as solvent at −20 °C, the yield was very low (Entry 5). Interestingly, the addition of water (DMF containing 10% H_2O) dramatically accelerated the reaction, resulting in the formation of **2a** in 82% yield with 25% ee. The reaction at −30 °C for 6 h slightly improved the enantioselectivity (33% ee, Entry 7), while a lower temperature (−40 °C) decreased the reaction rate (Entry 8). Results of control experiments in the absence of **A** or in the presence of either 2 molar equiv of γ-CD or a mixture of 2 molar equiv of γ-CD and 1 molar equiv of C_{60} without **A** clearly showed that not only was the reduction of **1a** greatly accelerated by the presence of **A**, but the asymmetric induction also occurred in the presence of the supramolecular fullerene complex (**A**) (Entries 9–11).[7] Unfortunately, the reaction did not proceed catalytically in **A** under the reaction conditions (Entries 12 and 13). Our separate study found that the photoreaction was included in the N_2 fixation assisted by **A**,[5] whereas in the present reaction no remarkable effect of light was observed (Entry 14).

Published on the web November 11, 2004; DOI 10.1246/bcsj.77.2047

Table 1. γ-Cyclodextrin-Bicapped C_{60} (**A**)-Mediated Asymmetric Reduction of Acetophenone (**1a**) with $NaBH_4$

Entry	**1a**/mmol	Additive/mmol	$NaBH_4$ /mmol	Solvent/mL	Temp. /°C	Time /h	GLC Yield/%	Ee/%[a]
1	0.027	**A** (0.027)	0.027	DMSO (10% H_2O) (2)	0	1	66	18
2	0.027	**A** (0.027)	0.054	DMSO (10% H_2O) (2)	0	1	82	20
3	0.027	**A** (0.027)	0.071	DMSO (10% H_2O) (2)	0	1	99	17
4	0.05	**A** (0.05)	0.15	H_2O (5)	0	3	52	2
5	0.05	**A** (0.05)	0.15	DMF (5)	−20	3	9	11
6	0.05	**A** (0.05)	0.15	DMF (10% H_2O) (5)	−20	3	82	25
7	0.05	**A** (0.05)	0.15	DMF (10% H_2O) (5)	−30	6	84[b]	33
8	0.05	**A** (0.05)	0.15	DMF (10% H_2O) (5)	−40	12	30[b]	33
9	0.05	—	0.15	DMF (10% H_2O) (5)	−20	3	6	0
10	0.05	γ-CD (0.10)	0.15	DMF (10% H_2O) (5)	−20	3	17	9
11	0.05	γ-CD (0.10) C_{60} (0.05)	0.15	DMF (10% H_2O) (5)	−20	3	49	16
12	0.05	**A** (0.025)	3.0	DMF (10% H_2O) (5)	−20	3	63	12
13	0.05	**A** (0.01)	3.0	DMF (10% H_2O) (5)	−20	3	24	16
14[c]	0.05	**A** (0.05)	3.0	DMF (10% H_2O) (5)	−20	3	69	20

a) Determined by GLC. Absolute configuration of a rich enantiomer is (*R*). b) Isolated yield. c) The reaction in the dark.



Scheme 1.

Table 2. γ-Cyclodextrin-Bicapped C_{60} (**A**)-Mediated Asymmetric Reduction of Ketones **1a**–**1l** with $NaBH_4$[a]

Entry	Product	Isolated yield/%	Ee/%[b]
1[c]	**2a**	84	38
2	**2b**	95	45
3[c]	**2b**	91	48
4[d]	**2b**	16	12
5[e]	**2b**	15	19
6	**2c**	68	30
7	**2d**	>99	23
8	**2e**	40	42
9	**2f**	>99	41
10	**2g**	72	47
11	**2h**	96	30
12	**2i**	54	21
13	**2j**	39	8
14	**2k**	68	2
15	**2l**	12	3

a) Under the same conditions of Entry 6 of Table 1. b) Determined by HPLC. c) At −30 °C for 6 h. d) In the presence of γ-CD instead of **A**. e) In the presence of a mixture of γ-CD and C_{60} instead of **A**.

Results of the asymmetric reduction of some prochiral aromatic ketones are shown in Table 2. Among the ketones **1** bearing different alkyl groups (R) (Entries 1–7), **1b** (R = isopropyl) showed the higher selectivity to give the corresponding alcohol **2b** in 95% yield with 45% ee (Entry 2). Again, the control experiments using either γ-CD or a mixture of γ-CD and C_{60} only showed a much lower selectivity and reactivity (Entries 4 and 5). Substituents on the benzene ring affected the reaction rate and the selectivity. Ketones with a methoxy group on aromatic nuclei showed nearly the same reactivity and selectivity as **1a** (Entries 8–10). In the case of **1h** and **1i** having a chloro substituent (Entries 11 and 12), a slight decrease of the selectivity was observed. On the other hand, a methyl substituent dramatically decreased both the product yield and the selectivity (Entries 13 and 14), although the reasons for such phenomena are not yet clear. Other ketones, such as isopropyl 2-naphthyl ketone, chalcone, and 2-octanone, also gave the corresponding alcohols in good yields with 15–20% ee (Fig. 2).

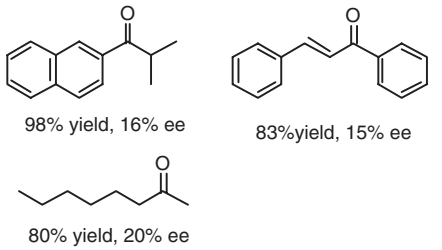
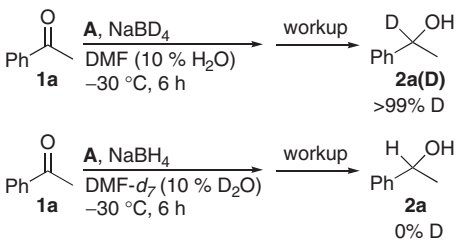


Fig. 2.



Scheme 2.

In order to investigate the reaction course, the reduction of **1a** with $NaBD_4$ in the presence of **A** was examined (Scheme 2). Almost complete incorporation of D in the product **2a**(**D**) was

observed by ^{1}H NMR. Furthermore, the reduction of **1a** with $NaBH_4$ in DMF-d_7 containing 10% D_2O gave **2a** without any deuterium incorporation. In the same way, the reduction of **1a** with $NaBD_4$ in DMSO (10% H_2O) afforded **2a**(**D**) (>99% D). These results suggest that the hydrogen source in this reduction system is derived from $NaBH_4$; that is, "hydride reduction" proceeded.[8] Although the detailed mechanisms of the effect of **A** as well as those of asymmetric induction are not yet clear, we assume that some reactive species might be formed by the reaction of **A** with $NaBH_4$ and that a subsequent hydride transfer to the carbonyl carbon occurred to give the product alcohol accompanied with the enantiotopos-differentiation in the belt region (hydrophobic part).[9,10]

In summary, we have demonstrated the supramolecular γ-cyclodextrin-bicapped C_{60} (**A**)-mediated asymmetric reduction of prochiral ketones. Although the enantioselectivity was not yet high in view of the recent development of excellent methods for asymmetric reduction of carbonyl compounds,[11] the results described herein may open a new field in fullerene chemistry.

Experimental

General Procedures. NMR spectra were recorded on JEOL EX-400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) and JNM-AL-300 (^{1}H NMR, 300 MHz; ^{13}C NMR, 75.5 MHz) instruments for solutions with Me_4Si as an internal standard. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F-254 plates. GLC analyses were performed on a Shimadzu GC-8A instrument (glass column packed with 10% Silicone SE-30® on Chromosorb® WAW DMCS 60/80, 2.0 m × 3.2 mm) with flame-ionization detectors (FID) and helium as carrier gas. The data were processed by a Shimadzu Chromatopac C-R6A calculator. Column chromatography on SiO_2 was performed with Wako Wakogel C-300, Kanto Silica gel 60. HPLC analyses were performed on an L-7000 instrument (HITACHI) using Daicel Chiralcel® AD, AS, and OD columns (4.6 × 250 mm) at 25 °C. All commercially available organic and inorganic compounds were used without further purification.

Synthesis of γ-Cyclodextrin-Bicapped C_{60} (A). Into a solution of γ-CD (1.2 g, 0.93 mmol) in hot water (ca. 80 °C, 60 mL) was carefully diffused a hot solution of C_{60} (400 mg, 0.56 mmol) in toluene (160 mL) without stirring. The mixture of two liquid phases was then vigorously stirred under reflux at 120 °C for 48 h. After cooling to room temperature without stirring, the purple precipitates were collected by a pipette into a 50 mL sample tube, and then some distilled water (ca. 30 mL) was added to it. The mixture was shaken well and the tube was allowed to stand until the complete precipitation of the purple solid. After decantation of the water containing excess γ-CD, the same washing procedure was repeated four times. Finally, the purple solids were collected by centrifugation and dried in vacuo by using the freeze dryer. The purple toluene layer containing unreacted C_{60} was reused for the next reaction in a similar way using a half amount of γ-CD (0.6 g, 0.47 mmol) in water (60 mL) to give the same precipitates. Unreacted C_{60} was again treated with γ-CD (0.6 g) and the purple **A** was totally obtained in 70% yield (1.46 g, 0.39 mmol).

Typical Procedure for the Reduction of Ketones. A mixture of purple powder **A** (0.05 mmol) and DMF (10% H_2O) (3.0 mL) in a 10-mL two-necked flask was stirred at room temperature under N_2. After cooling to −20 °C, $NaBH_4$ (0.15 mmol) in DMF (10% H_2O) (2.0 mL) was added to the reaction mixture. After stirring for a few minutes, a ketone (0.05 mmol) was added and the mixture was stirred at −20 °C. After 3 h, the mixture was extracted with diethyl ether and the organic layer was washed with water. The ethereal solution was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to give an oil, which was subjected to column chromatography on SiO_2 with EtOAc/*n*-hexane (2/98) as eluent. The enantiomeric excess was determined by HPLC or GLC. Reduction of ketones **1a**–**1l** in the absence of **A** gave only a small amount of the product alcohol (1–6% yield) in all cases under the reaction conditions shown in Table 2.

This work was supported by a Grant-in-Aid for Scientific Research (No. 13305062) from the Ministry of Education, Culture, Sports, Science and Technology, and by the JSPS FY 2002 "Research for the Future Program".

References

1 F. Diederich and M. Gómez-López, *Chem. Soc. Rev.*, **28**, 263 (1999).

2 Z. Yoshida, H. Takekuma, S. Takekuma, and Y. Matsubara, *Angew. Chem., Int. Ed. Engl.*, **33**, 1597 (1994).

3 For examples of γ-CD and C_{60} inclusion complex, see: a) T. Andresson, K. Nilsson, M. Sundahl, G. Westman, and O. Wennerström, *J. Chem. Soc., Chem. Commun.*, **1992**, 604. b) D. D. Zhang, J. W. Chen, Y. Y. Yang, R. F. Cai, X. L. Shen, and S. H. Wu, *J. Inclusion Phenom.*, **16**, 245 (1993). c) K. Kanazawa, H. Nakanishi, Y. Ishizuka, T. Nakamura, and M. Matsumoto, *Fullerene Sci. Technol.*, **2**, 189 (1993). d) K. I. Priyadarsini, H. Mohan, A. K. Tyagi, and J. P. Mitteal, *J. Phys. Chem.*, **98**, 4756 (1994). e) T. Braun, Á. Buvári-Barcza, L. Barcza, I. Konkoly-Thege, M. Fodor, and B. Migali, *Solid State Ionics*, **74**, 47 (1994). f) V. Ohlendorf, A. Willnow, H. Hungerhühler, D. M. Guldi, and K. D. Asmus, *J. Chem. Soc., Chem. Commun.*, **1995**, 759. g) K. Komatsu, K. Fujiwara, Y. Murata, and T. Braun, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2963. h) C. N. Murthy and K. E. Geckeler, *Chem. Commun.*, **2001**, 1194.

4 a) S. Takekuma, H. Takekuma, T. Matsumoto, and Z. Yoshida, *Tetrahedron Lett.*, **41**, 1043 (2000). b) S. Takekuma, H. Takekuma, T. Matsumoto, and Z. Yoshida, *Tetrahedron Lett.*, **41**, 2929 (2000).

5 Nitrogen fixation assisted by **A** has been found by our group, see: Y. Nishibayashi, M. Saito, S. Uemura, S. Takekuma, H. Takekuma, and Z. Yoshida, *Nature*, **428**, 279 (2004).

6 Complex **A** could not be recovered after the reaction. Its structure may be changed during the reaction.

7 The example of the asymmetric reduction by $NaBH_4$ of ketone–β-cyclodextrin complexes, see: a) N. Baba, Y. Matsumura, and T. Sugimoto, *Tetrahedron Lett.*, **19**, 4281 (1978). b) R. Fornasier, F. Reniero, P. Scrimin, and U. Tenellato, *J. Org. Chem.*, **50**, 3209 (1985). c) M. A. Reddy, N. Bhanumathi, and K. R. Rao, *Chem. Commun.*, **2001**, 1974.

8 The generation of C_{60}^{2-} could be also detected in DMF (10% H_2O) by a near-IR spectrum.

9 Since a near-IR spectrum of $C_{60}H^-$ produced by the protonation of C_{60}^{2-} was suggested to be similar to that of C_{60}^- by Bard et al.,[10] it is not ruled out that the near-IR spectrum of C_{60}^{2-}, which was previously observed by us,[4a] might be similar to that of $C_{60}H^{2-}$ and it might act as a reduction species.

10 D. E. Cliffel and A. J. Bard, *J. Phys. Chem.*, **98**, 8140 (1994).

11 Recent examples of asymmetric reduction by MBH_4 (M = Li, Na) using a chiral dendrimer or a chiral Lewis acid, see: a) J. T. Suri, T. Vu, A. Hernandez, J. Congdon, and B. Singaram, *Tetrahedron Lett.*, **43**, 3649 (2002). b) A. R. Schmitzer, S. Franceschi, E. Perez, I. Rico-Lattes, L. Thion, M. Erard, and C. Vidal, *J. Am. Chem. Soc.*, **123**, 5956 (2001).