Dalton Transactions

Inclusion of alkyl nitriles by tetra-armed cyclen with styrylmethyl groups

Journal:	*Dalton Transactions*
Manuscript ID	DT-ART-01-2020-000335.R1
Article Type:	Paper
Date Submitted by the Author:	04-Feb-2020
Complete List of Authors:	Ju, Huiyeong; Toho University, Chemistry Tenma, Honoka; Toho University, Chemistry Iwase, Miki; Toho University, Chemistry Lee, Eunji; Toho University, Chemistry Ikeda, Mari; Chiba Institute of Technology, Education Center, Faculty of Engineering Kuwahara, Shunsuke; Toho University, Department of Chemistry Habata, Yoichi; Toho University, Chemistry; Toho University, Research Center for Materials with Integrated Properties

ARTICLE

Inclusion of alkyl nitriles by tetra-armed cyclen with styrylmethyl groups

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Huiyeong Ju,[a] Honoka Tenma,[a] Miki Iwase,[a] Eunji Lee,[a] Mari Ikeda,[c] Shunsuke Kuwahara[ab] and Yoichi Habata*[ab]

Synthesis of tetra-armed cyclens (**2a**–**2e**), with substituted styrylmethyl groups as side-arms, and their Ag^+ complexes are reported. The Ag^+ complex with tetra styrylmethyl-armed cyclen (**2a**) incorporates alkyl nitriles in a *pseudo*-cavity formed by the four styrylmethyl side-arms. This prompted us to apply this system to the determination of the absolute configurations of chiral nitriles with low $[\alpha]_D$ and low circular dichroism (CD) intensity. In the CD spectra of the **2a**/Ag^+ complex, (*S*)- and (*R*)-**G1** did not show a specific Cotton effect. While, when chiral nitriles were added to the **2a**/Ag^+ complex, drastic spectral changes were observed. The (*S*)-**G1**@**2a**/Ag^+ system exhibited first a negative and then a positive Cotton effect, meanwhile the (*R*)-**G1**@**2a**/Ag^+ system shows the mirror image of (*S*)-**G1**@**2a**/Ag^+. We have, therefore, demonstrated a new technique for determining the absolute configuration of weak optical rotation molecules using the Ag^+ complex with **2a**.

Introduction

The cyano group (-CN) is a versatile functional group which is present not only in intermediates in organic synthesis, but also in many medicinal drugs.[1-5] For example, nitriles can be converted easily to carboxylic acids, amides, amines, aldehydes, and other groups.[1-3] In medicinal chemistry, more than 30 nitrile-containing pharmaceuticals are prescribed for a diverse array of medicinal indications.[4,5] Determination of their absolute configurations is especially important in the case of chiral nitriles. Enantiomers exhibit different biological activities and toxicity due to enantioselective interactions in chiral environments. The increased development of single-enantiomer pharmaceuticals has enhanced the need for rapid and convenient methods for chiral recognition and determination of the enantiomeric excess of chiral compounds. There are various methods for chiral analysis such as circular dichroism (CD), polarimetry, UV-vis, near-IR, NMR, optically active Raman, fluorescence spectroscopy, and chiral induced photoluminescence (CIP).[6-17] Ravinder *et al.* reported the determination of enantiomeric excess and absolute configuration of cyanohydrins, where CN and OH groups are directly bonded to the chiral carbon, by a chiral shift reagent and ^{1}H NMR.[17] However, reports on the assignment of the absolute configurations of various chiral alkyl nitriles are still rare. Furthermore, it is difficult to determine the absolute configurations and enantiomeric excess in chiral compounds with low $[\alpha]_D$ and low CD intensity. Therefore, the development of practical techniques for the measurement of weak optical rotation is becoming increasingly important, especially as X-ray crystallography shows the information on the absolute configurations directly only when single crystals are obtained.

Cyclen has been widely used as a binding site in metal ion sensors, a building block for supramolecular structures, catalytic drugs, chirality signalling and in fluorescent probes for imaging.[18-30] Shinoda *et al*. reported that a Ca^{2+} complex with cyclen with three pyridine and one triazole side-arms can act as a chirality-transfer reagent from an anion source. An effective mediator for the chirality-rewriting cycle was reported using the Ca^{2+} complex.[23] Tsukube *et al.* reported a series of Na^+, Ca^{2+}, and La^{3+} complexes with octadentate-armed cyclen. Among them, the Ca^{2+} complex formed 1:1 adducts with the organic carboxylate anions in solution, which functioned as an effective CD probe to determine the enantiomeric excess (ee%) of the chiral anions.[24]

We have previously reported[25-30] that tetra-armed cyclens with aromatic side-arms behave like an insectivorous plant (Venus flytrap) when they form complexes with Ag^+. The aromatic side-arms in the armed-cyclens cover the Ag^+ incorporated into the cyclen cavities by Ag^+–π and CH–π interactions. We called the armed cyclens "*argentivorous molecules*" (Fig. 1).[31] Following on from our previous work, we propose the synthesis of tetra-armed cyclens (**2a**-**2e**) with styrylmethyl groups to form Ag^+ complexes. We expected that silver(I) complex with cyclens having styrylmethyl side-arms form a *pseudo*-cavity by the side-arms to afford an inclusion complex with a coordinating guest such as acetonitrile. (Fig. 1). Here we report the inclusion of alkyl nitriles with new armed cyclen.

[a] *Department of Chemistry and* [b]*Research Centre for Integrated Properties, Faculty of Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan. E-mail: habata@chem.sci.toho-u.ac.jp*
[b] *Department of Chemistry, Education Center, Faculty of Engineering, Chiba Institute of Technology, 2-1-1 Shibazono, Narashino, Chiba 275-0023, Japan*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: Synthesis, NMR spectra, crystal structures, CD spectra and UV-vis spectra. X-ray data of CCDC reference numbers 1974350 (**2a**), 1974351 (**2a**/Ag^+), 1974352 (**2a**/Cd^{2+}), 1974353 (**2a**/Co^{2+}), 1974354 (**2b**/Ag^+) 1974355 (**2c**/Ag^+), 1974357 (**2d**) and 1974358 (**2e**). See DOI: 10.1039/x0xx00000x

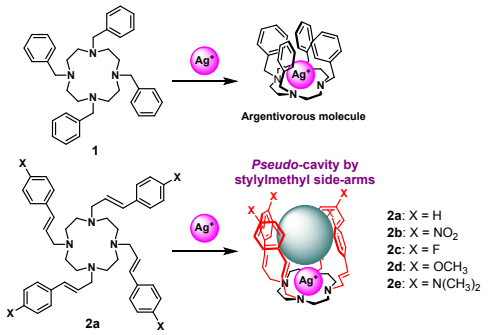

Fig. 1 Argentivorous molecules with benzyl cyclen (**1**) and styrylmethyl cyclens (**2a**-**2e**).

Considering the affinity of the cyano group with Ag^+ atoms, chiral nitriles with low $[\alpha]_D$ (**G1–G5** in Fig. 6 and Table S1) were used as guests. Furthermore, we report the discrimination ability of the Ag^+ complex towards several types of chiral nitriles through CD and ^1H NMR spectroscopy (Fig. 2). To the best of our knowledge, this is a rare demonstration of the use of an achiral host to determine absolute configuration.

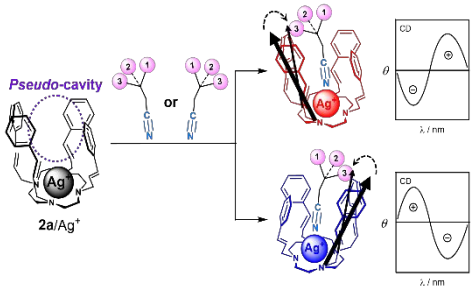

Fig. 2 Expected mechanisms for determining absolute configurations by forming complexes of chiral nitriles with the **2a**/Ag^+ complex. The numbering (1, 2, and 3) of substituents in guest molecules indicate priority in the Cahn-Ingold-Prelog rule (1 is the highest priority). Right: exciton coupling pattern of CD spectroscopy.[32,33]

Results and discussion

Synthesis and structural description of tetra-armed cyclens with substituted styrylmethyl groups

New tetra-armed cyclens (**2a**–**2e**, Scheme S1) were prepared by reductive amination of cyclen with the corresponding aromatic aldehydes in the presence of $NaBH(OAc)_3$. The structures of the new compounds were confirmed by ^1H and ^{13}C NMR spectroscopy, FAB-MS, elemental analysis and X-ray crystallography (Fig. S1–S7). On one hand, the cyclens **2a** and **2d** are present as the 1,2-alternate conformation, which is the same as that reported previously.[25,26] On the other hand, the crystal structure of **2e** reveals a 1,3-alternate conformation (Fig .S7). Each molecule **2e** participates in C-H–π interactions and hydrogen bonds, which contribute to the stability of the 1,3-alternate conformation structure (Fig. S7).

Structural description of silver(I) complexes

Crystalline products of **2a**/$AgPF_6$, **2b**/$AgCF_3SO_3$, and **2c**/$AgCF_3SO_3$ complexes were prepared and structurally confirmed by single-crystal X-ray diffraction (Fig. 3, S8-S10). As we expected, the four aromatic side-arms cover the Ag^+ ion incorporated into the ligand cavity. In the packing structure, a mixture of *Δ* and *Λ* forms were observed (Fig. 3a). In **2a**/$AgPF_6$, Ag1–C10, Ag1–C19, Ag1–C28, and Ag1–C37 distances are 3.353, 3.506, 3.391, and 3.423 Å, respectively. The distances indicate that the strength of the Ag^+–π interaction depends on the electron densities on the ethylene components.[34] In addition, the distances between the hydrogen atoms of acetonitrile and the adjacent benzene planes are in the range 2.155–2.880 Å. The distances are typical CH–π bond distances (Fig. S8).[35-38] Similarly, **2b**/$AgCF_3SO_3$ and **2c**/$AgCF_3SO_3$ show that the four aromatic side-arms cover the Ag^+ ion incorporated into the ligand cavity, even with electron-withdrawing groups such as NO_2 and F. (Fig. S9 and S10). In contrast, the side-arms in the **2a**/$Cd(NO_3)_2$ and **2a**/$Co(NO_3)_2$ complexes do not cover the metal(II) ions incorporated into the cyclen moiety (Fig. S11). As we expected, the X-ray structures show Ag^+ selectivity of tetra-armed cyclen with aromatic side-arms.

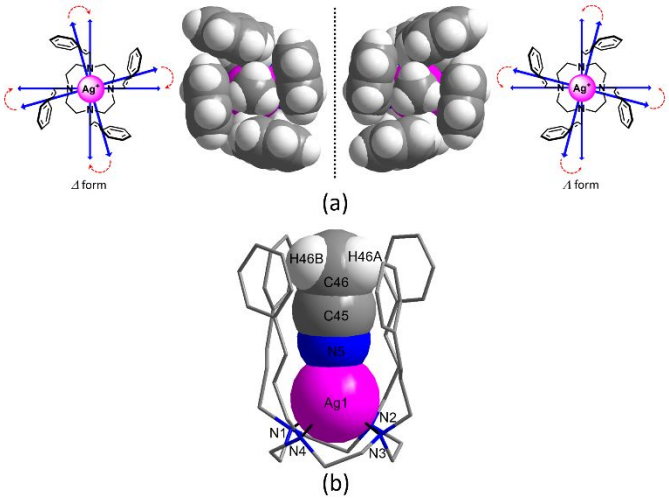

Fig. 3 Definition of the *Δ* and *Λ* forms in tetra-armed cyclens. X-ray structure of **2a**/$AgPF_6$: (a) top and (b) side view. Non-coordinated anions are omitted.

Ag^+ ion-induced ^1H NMR chemical shift changes were carried out to confirm the structures of the Ag^+ complexes in solution (Fig. 4 and S12). On the stepwise addition of AgOTf to a solution of **2a**, H_b protons in the side-arms shifted to a higher field by *ca*. 0.03 ppm, as the H_b protons are located in the shielded area next to the aromatic side-arm in solution. The H_a and H_c protons in the side-arms also shifted to a lower field by *ca*. 0.16 and 0.12 ppm, respectively. As presented above, the X-ray structure of the **2a**/$AgPF_6$ complex indicates that the H_a protons are located in a deshielded area next to the styrylmethyl side-arms. The chemical shift changes stopped at a metal:ligand ratio of 1:1, indicating that the complex formed has a stable 1:1 metal-to-ligand species. These ^1H NMR titration experiments support the observation that the aromatic side-arms cover the Ag^+ ions incorporated in the ligand cavity. When ligands **2b**–**2e** were used, similar chemical shift changes were observed (Fig. S13–16).

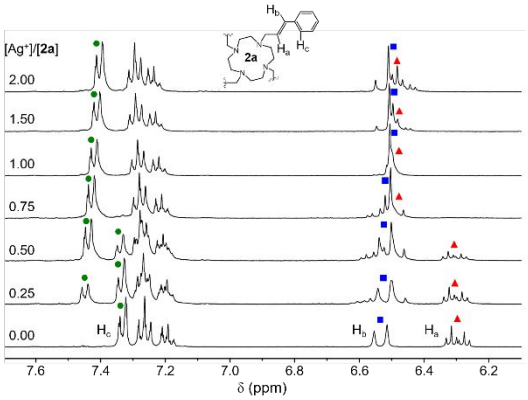

Fig. 4 Ag^+ ion-induced ^1H NMR shift changes of **2a** in a mixture of CD_2Cl_2 and CD_3OD (red triangle: H_a, blue rectangle: H_b, and green circle: H_c).

In the structure of the Ag^+ complex, we found that the styrylmethyl side-arms form a *pseudo*-cavity which can bind an acetonitrile molecule. The X-ray structure prompted us to investigate the interaction between the Ag^+ complex and acetonitrile. A comparative ^1H NMR study was carried out to confirm the inclusion phenomena in solution (Fig. 5 and S17). When the CH_3CN was added to **2a**, no chemical shift changes were observed (Fig. 5b). When the CH_3CN was added to Ag^+, the methyl proton signal shifted to a lower field by 0.09 ppm, as the acetonitrile molecules coordinate to Ag^+ (Fig. 5c). In the case of a mixture of CH_3CN, **2a**, and Ag^+, the methyl signal shifted to a higher field by 0.23 ppm (Fig. 5d), as the methyl protons are located in the shielded area of the styrylmethyl side-arms. When D_2O was added to a solution of CH_3CN+**2a**+Ag^+ (Fig. 5e), the broad-singlet at *ca.* 2.1 ppm disappeared, confirming that this signal is due to water from the complex. The NMR study suggests that the **2a**/Ag^+ complex incorporates CH_3CN in the *pseudo*-cavity by the styrylmethyl side-arms. On the other hand, no chemical shift changes of the methyl protons of CH_3CN were observed (Fig. S18) in the **1**/Ag+ complex. This comparative NMR study clearly shows that the benzyl side-arms doesn't form a *pseudo*-cavity. The log*K* value between **2a**/Ag^+ and CH_3CN was measured by titration experiment using ^1H NMR and estimated as ca. 2.1 (Fig. S19). When more bulky nitriles, such as propionitrile, isobutyronitrile, and pivalonitrile, were used, the **2a**/Ag^+ complex also formed inclusion complexes (Fig. S20 for ^1H NMR and Table S2 for log*K*). These results indicate that the cavity of the **2a**/Ag^+ can bind alkyl nitriles with bulky substituents.

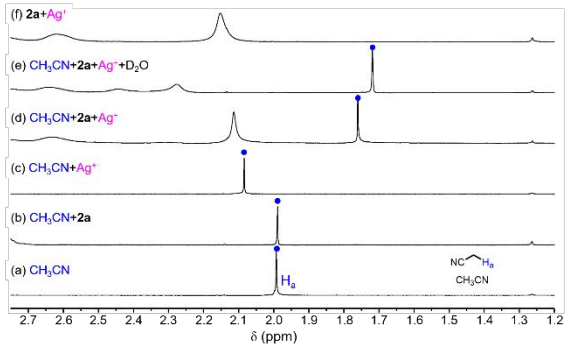

Fig. 5 Comparative ^1H NMR spectra of (a) CH_3CN, (b) CH_3CN+**2a**, (c) CH_3CN+Ag^+, (d) CH_3CN+**2a**+Ag^+, (e) CH_3CN+**2a**+Ag^++D_2O, and (f) **2a**+Ag^+ in a mixture of CD_2Cl_2 and CD_3OD.

Assignment of the absolute configuration s of chiral nitriles

The SCXRD and NMR results of **2a**/Ag^+ complex prompted us to apply this system to the determination of the absolute configurations of chiral nitriles with low $[\alpha]_D$ and low CD intensity. To select chiral nitriles used in this system, we first measured CD spectra of several chiral nitriles as shown in Fig. 6 and Table S1. When a 3.00 x 10^{-3}M solution of a chiral cyanohydrin (**G6**) was used (Fig. S21), a considerable Cotton effect was observed owing to the aromatic ring. On the other hand, chiral nitriles **G1**-**G5** did not show a significant Cotton effect even under 30.0 x 10^{-3} M solution. We, therefore, used chiral nitriles **G1**-**G5** as a guest in this system.

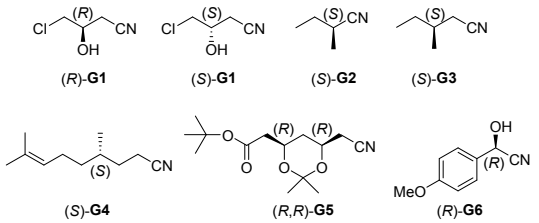

Fig. 6 Structure of chiral nitriles as a guest (**G1**-**G6**).

To investigate the interactions between the Ag^+ complexes and a chiral guest **G1** in solution, ^1H NMR titration experiments using (*S*)-**G1** and (*R*)-**G1** were carried out in CD_2Cl_2/CD_3OD (Fig. S22). On stepwise addition of (*S*)-**G1** and (*R*)-**G1** to the Ag^+ complex solutions, the H_c protons shifted to a higher field by *ca*. 0.04 ppm, as the H_c protons are located in the shielded area in solution. The H_d and H_e protons also shifted to a lower field by *ca*. 0.02 and 0.03 ppm, respectively. All signals in these ^1H NMR titration experiments show the same shaped peak, which infers that there is one chemical species in solution. From the titration data, the log*K* values between the Ag^+ complexes with (*S*)-**G1** and (*R*)-**G1** in CD_2Cl_2/CD_3OD were estimated to be 1.7 and 1.8, respectively (Fig. S23). The interaction between the **2a**/Ag^+ and (*S*)-**G1** was further confirmed by 2D diffusion-ordered spectroscopy (DOSY) ^1H NMR experiments (Fig. S24).[39-41]

In order to investigate the CD spectral changes depending on the addition of chiral nitriles, CD spectra of the **2a**/Ag^+ complex with chiral nitriles were carried out in EtOH/1,4-dioxane (9/1) solution (Fig. 7). In the CD spectra of the **2a**/Ag^+ complex, no Cotton effect

was observed as **2a** is achiral. The CD Spectra of (*S*)- and (*R*)-**G1** did not show a specific Cotton effect under these conditions. In contrast, drastic spectral changes were observed when chiral nitriles were added to the **2a**/Ag^+ complex. As shown in Fig. 7, the (*S*)-**G1@2a**/Ag^+ system exhibited first a negative (λ_{ex} = 260 nm [θ = +15000]) and then a positive (λ_{ex} = 235 nm [θ = –4000]) Cotton effect, whereas the (*R*)-**G1@2a**/Ag^+ system shows the mirror image of the Cotton effect of (*S*)-**G1@2a**/Ag^+. When the above procedure was carried out using different metal ions (Hg^{2+}, Cu^{2+} and Zn^{2+}), no CD spectral changes were observed (Fig. S25a). These results also indicate that only the Ag^+ complex can incorporate chiral nitrile guests in the *pseudo*-cavity. UV-vis measurements demonstrated that the Cotton effects were observed in the range of the absorption of styrylmethyl groups. (Fig. 7b and S25b). These CD and UV-vis spectral data exhibit a significant CD Cotton effect due to the exciton coupling[32,33] between the styrylmethyl groups in **2a**. Therefore, the four styrylmethyl groups constitute counterclockwise and clockwise screw senses in (*R*)-**G1@2a**/Ag^+ and (*S*)-**G1@2a**/Ag^+, respectively.

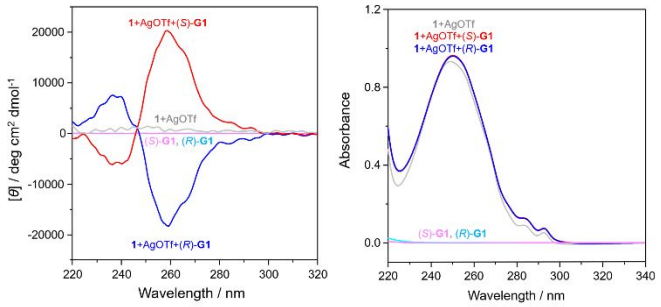

Fig. 7 (a) CD ([**G**]= 30.0 x 10^{-3} M, [**2a**] = [AgOTf] = 3.00 x 10^{-3} M) and (b) UV-vis spectra ([**G**]= 15.0 x 10^{-5} M, [**2a**] = [AgOTf] = 1.50 x 10^{-5} M) of **2a**/Ag^+ complex, chiral **G1** and chiral **G1@2a**/Ag^+. Solvent (EtOH/1,4-dioxane (9/1)).

To evaluate the effectiveness for quantitative enantiomeric excess (ee) determination of chiral nitriles, a calibration curve was created using (R)-**G1** and (S)-**G1** with varying ee (–100, –60, –20, 0, +20, +60, +100 %ee of (S)-**G1**). The molar ellipticities (θ) at 260 nm were plotted versus %ee (Fig. 8). The calibration curve shows a linear relationship, with R^2 = 0.99, indicating that this system would be applicable to quantitative ee determination of chiral nitriles with low molar ellipticity.

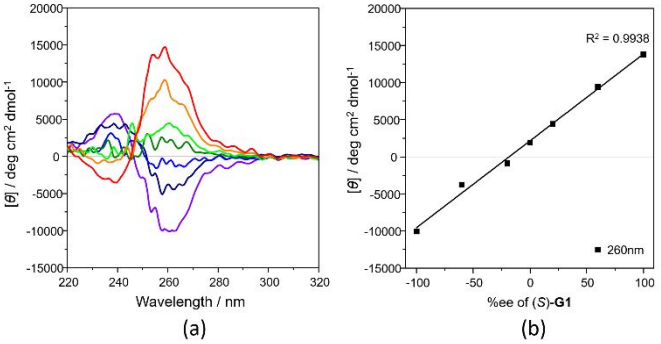

Fig. 8 (a) CD spectra (EtOH/1,4-dioxane, 273 K, [**2a**/Ag^+] = 3.00 x 10^{-3} M) of **2a**/Ag^+ in presence of **G1** (30.0 x 10^{-3} M) with various *ee* values and (b) the corresponding *ee* calibration plots at 260 nm.

The (*S*)-**G1**-induced CD spectral changes were carried out to estimate the log*K* value between the **2a**/Ag^+ complex and (*S*)-**G1** in EtOH/1,4-dioxane as a different solvent system (CD_2Cl_2/CD_3OD) was used for the ^{1}H NMR experiments (Fig. S9). The log*K* was estimated to be ca. 1.6, and this value is approximately the same as the log*K* from the ^{1}H NMR titration experiments.

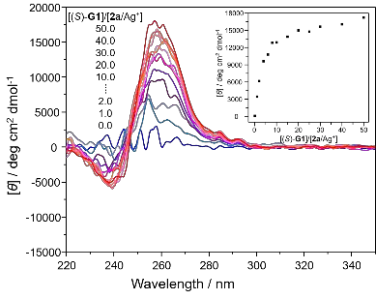

Fig. 9 CD spectral changes of **2a**/Ag^+ complex (3.00 x 10^{-3} M) upon addition of (*S*)-**G1** in EtOH/1,4-dioxane (9/1). (Inset) titration curve at 264 nm.

To confirm the versatility of the chirality determination system, the same experiments were performed using the following nitriles (Fig. S26 and S27); a cyano group bonded directly to chiral carbon ((*S*)-**G2**)), a cyano group bonded to carbon next to chiral carbon ((*S*)-**G3**)) and a cyano group bonded to the second carbon from chiral carbon ((*S*)-**G4**; Fig. 10b). Interestingly, initially positive then negative Cotton effects were observed when (*S*)-**G3** and (*S*)-**G4** were used (Fig. 10a). However, the opposite Cotton effect was observed with (*S*)-**G2**. These results are explained as follows: In the case of (*S*)-**G3** and (*S*)-**G4** with methylene and dimethylene groups between the cyano group and the chiral carbon, respectively, the cyanoalkyl groups act as a chiral barrier so the Cahn-Ingold-Prelog rule can be applied to the four substituents bound to the chiral carbons. However, the cyano group in (*S*)-**G2** does not act as a chiral barrier as the cyano group coordinates to Ag^+ directly. The priority rule, therefore, must be applied with the remaining three substituents (CH_3CH_2- >CH_3- > H-), excluding the cyano group. The styrylmethyl arms constitute a counterclockwise screw sense and so the Cotton effect in the (*S*)-**G2** system would present as that of the (*R*)-**G2** system (Fig. 10c).

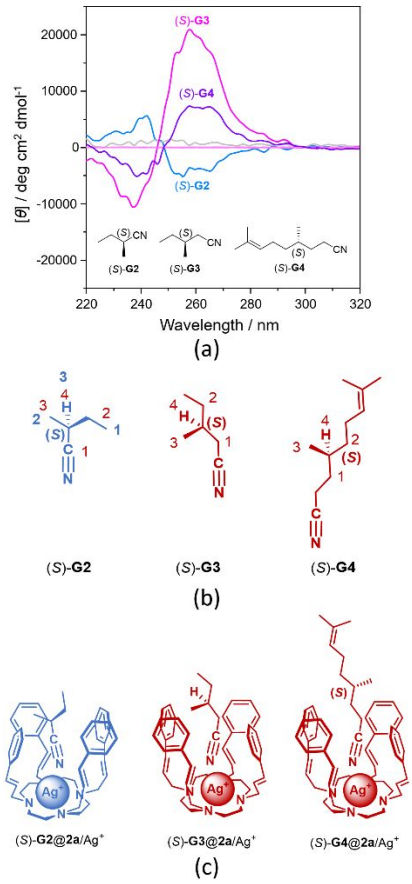

Fig. 10 (a) CD spectra of (*S*)-**G2**, **G3** and **G4** and their complexes with **2a**/Ag^+, (b) Structures of (*S*)-**G2**, **G3** and **G4** with priorities and (c) Postulated structures of the chiral guests@**2a**/Ag^+ complexes.

This system also can be applied to chiral amines **G7**-**G10** (Fig. S28-S31 and Table S4), and the CD patterns for (*S*)- and (*R*)-amines were the same with those of chiral nitriles.

Experimental

General information

Melting points were obtained with a Mel-Temp capillary apparatus and were not corrected. FAB mass spectra were obtained using a JEOL 600 H mass spectrometer. ^{1}H NMR and ^{13}C spectra were measured on a JEOL ECP400 (400 MHz) spectrometer. 2D-DOSY ^{1}H NMR spectra were measured on a Bruker Avance400 (400 MHz) spectrometer. UV-vis spectra were recorded on a JASCO V-650 spectrometer. CD spectra were recorded on a JASCO J-820 spectrometer. Polarimeter were recorded on a JASCO P2200 spectrometer. Cyclen was purchased from Macrocyclics. All reagents were standard analytical grade and were without further purification.

Synthesis of 1,4,7,10-tetracinnamyl-1,4,7,10-tetraazacyclododecane (2a)

After a mixture of 1,4,7,10-tetraazacyclododecane (0.269 g, 1.56 mmol), cinnamaldehyde (1.67 g, 12.6 mmol) and $NaBH(OAc)_3$ (2.05 g, 9.68 mmol) in 1,2-dichloroethane (25 mL) was stirred for 4 days at room temperature under nitrogen atmosphere (atmospheric pressure), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using 5:2 toluene/ethanol to 10:1 toluene/ethanol to 10:9:1 toluene/ethanol/ammonia as solvent gradient. Flash column chromatography afforded the product as a yellow solid in 36% yield. Mp: 120–120.5 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 7.24 (*t*, *J* = 1.60 Hz, 8H), 7.19 (*t*, *J* = 1.60 Hz, 8H), 7.12 (*d*, 4H), 6.49 (*s*, 2H), 6.44 (*s*, 2H), 6.24 (*s*, 2H), 6.19 (*s*, 2H), 3.14 (*s*, 4H), 2.65 (*s*, 16H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 137.9, 132.1, 129.1, 128.9, 127.5, 126.6, 58.5, 53.3. FAB-MS (m/z) (matrix: DDT): 638 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{44}H_{52}N_4$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.82; H, 8.20; N, 8.62.

Synthesis of 1,4,7,10-tetra(4-nitrocinnamyl)-1,4,7,10-tetraazacyclododecane (2b)

After a mixture of 1,4,7,10-tetraazacyclododecane (0.184 g, 1.07 mmol), 4-nitrocinnamaldehyde (1.54g, 8.69 mmol) and $NaBH(OAc)_3$ (1.81 g, 8.54 mmol) in acetonitrile (25 mL) was stirred for 7 days at room temperature under nitrogen atmosphere (atmospheric pressure), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using 5:2 toluene/ethanol to 10:9:1 toluene/ethanol/ammonia to 5:1:0.2 chloroform:methanol:ammonia as solvent gradient. Flash column chromatography afforded the product as a yellow solid in 37% yield. Mp: 162.0-164.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.7 Hz, 8H), 7.41 (d, *J* = 8.6 Hz, 8H), 6.64 (d, *J* = 8.0 Hz, 4H), 6.45 (dt, *J* = 15.8 Hz, *J* = 6.1 Hz, 4H), 3.27 (d, *J* = 5.7 Hz, 8H), 2.76 (s, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 143.5, 133.3, 130.1, 126.6, 124.0, 57.9, 53.0. FAB-MS (matrix thioglycerol): *m/z* 817 ($[M+H]^+$, 6%). Anal. Calcd. for $C_{44}H_{48}N_8O_8$: C, 64.69; H, 5.92 ; N, 13.72. Found: C, 64.60; H, 6.09; N, 13.51.

Synthesis of 1,4,7,10-tetra(4-fluorocinnamyl)-1,4,7,10-tetraazacyclododecane (2c)

After a mixture of 1,4,7,10-tetraazacyclododecane (0.244 g, 1.41 mmol), 4-fluorocinnamaldehyde (1.74g, 11.6mmol) and $NaBH(OAc)_3$ (2.17 g, 10.3 mmol) in 1,2-dichloroethane (25 mL) was stirred for 7 days at room temperature under nitrogen atmosphere (atmospheric pressure), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using 10:9 toluene/ethanol to 10:9:1 toluene/ethanol/ammonia as solvent gradient. Flash column chromatography afforded the product as a white solid in 55% yield. Mp: 122.9-124.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (q, *J* = 4.7 Hz, 10H), 6.95 (t, *J* = 8.7 Hz, 8H), 6.46 (d, *J* = 16.0 Hz, 4H), 6.17 (dt, *J* = 15.9 Hz, *J* = 6.5 Hz, 4H), 3.20 (d, *J* = 6.3 Hz, 8H), 2.74 (s, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, $^1J_{CF}$ = 246.2 Hz), 133.4 (d, $^4J_{CF}$ = 3.1 Hz), 130.8,

127.8 (d, $^5J_{CF}$ = 2.3 Hz), 127.7 (d, $^3J_{CF}$ = 7.9 Hz), 115.4 (d, $^2J_{CF}$ = 21.7 Hz), 58.1, 52.5. FAB-MS (matrix DTT/TG = 1:1): *m/z* 709 ([M+H]$^+$, 5%). Anal. Calcd. for $C_{44}H_{48}F_4N_4$: C, 74.55; H, 6.83; N, 7.90. Found: C, 74.46; H, 7.07; N, 7.89.

Synthesis of 1,4,7,10-tetra(4-methoxycinnamyl)-1,4,7,10-tetraazacyclododecane (2d)

After a mixture of 1,4,7,10-tetraazacyclododecane (0.232 g, 1.32 mmol), 4-methoxycinnamaldehyde (1.71 g, 10.6 mmol) and $NaBH(OAc)_3$ (2.12 g, 10.0 mmol) in 1,2-dichloroethane (25 mL) was stirred for 7 days at room temperature under nitrogen atmosphere (atmospheric pressure), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using 10:9 toluene/ethanol to 10:9:1 toluene/ethanol/ammonia as solvent gradient. Flash column chromatography afforded the product as a white solid in 84% yield. Mp: 153.1-154.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dt, *J* = 8.7 Hz, *J* = 2.4 Hz, 9H), 6.81 (dt, *J* = 8.8 Hz, *J* = 2.6 Hz, 8H), 6.42 (d, *J* = 15.9 Hz, 4H), 6.14 (dt, *J* = 15.8 Hz, *J* = 6.6 Hz, 4H), 3.79 (s, 12H), 3.20 (d, *J* = 6.3 Hz, 8H), 2.74 (s, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 131.5, 130.1, 127.4, 125.8, 113.9, 58.3, 55.2, 52.2. FAB-MS (matrix glycerine): *m/z* 757 ([M+H]$^+$, 10%). Anal. Calcd. for $C_{48}H_{60}N_4O_4$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.14; H, 8.22; N, 7.37.

Synthesis of 1,4,7,10-tetra(4-dimethylaminocinnamyl)-1,4,7,10-tetraazacyclododecane (2e)

After a mixture of 1,4,7,10-tetraazacyclododecane (0.210 g, 1.24 mmol), 4-dimethylaminocinnamaldehyde (1.74 g, 9.92 mmol) and $NaBH(OAc)_3$ (2.13 g, 10.0 mmol) in 1,2-dichloroethane (25 mL) was stirred for 7 days at room temperature under nitrogen atmosphere (atmospheric pressure), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using 10:9 toluene/ethanol to 10:9:1 toluene/ethanol/ammonia as solvent gradient. Flash column chromatography afforded the product as a white solid in 69% yield. Mp: 186.0-188.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.5 Hz, 8H), 6.65 (d, *J* = 8.5 Hz, 8H), 6.38 (d, *J* = 15.8 Hz, 4H), 6.09 (dt, *J* = 15.7 Hz, *J* = 6.5 Hz, 4H), 3.20 (d, *J* = 6.3 Hz, 8H), 2.94 (s, 24H), 2.75 (s, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 132.1, 127.2, 126.0, 123.5, 112.5, 58.5, 52.0, 40.6. FAB-MS (matrix DTT/TG = 1:1): *m/z* 808 ([M]$^+$, 2%). Anal. Calcd. for $C_{52}H_{72}N_8$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.19; H, 9.16; N, 13.76.

Synthesis of 2a/$AgPF_6$

$AgPF_6$ (15.2 mg, 0.060 mmol) in MeOH (1 mL) was added to a solution of **2a** (38.6 mg, 0.061 mmol) in dichloromethane (1 mL). The colourless precipitate obtained was filtered and dissolved in acetonitrile. Vapor diffusion of methanol into the acetonitrile solution afforded a colourless crystalline product **2a**/$AgPF_6$ suitable for X-ray analysis. Mp: 155.5 °C (dec.). Anal. Calcd. For$C_{46}H_{55}N_5AgPF_6$: C, 59.36; H, 5.96 ; N, 7.52. Found: C, 59.23; H, 5.76; N, 7.49.

Synthesis of 2a/$Cd(NO_3)_2$

$Cd(NO_3)_2$ (4.77mg, 0.016 mmol) in methanol (1 mL) was added to a solution of **2a** (10.0 mg, 0.016 mmol) in 1,2-dichloroethane (1 mL). Slow evaporation of the solution afforded a colourless crystalline product **2a**/$Cd(NO_3)_2$ suitable for X-ray analysis. Mp: 255.0 °C (dec.). Anal. Calcd. For $C_{45}H_{54}CdClN_6O_6$: C, 58.57; H, 5.90 ; N, 9.11. Found: C, 58.86; H, 5.90 ; N, 9.39.

Synthesis of 2a/$Co(NO_3)_2$

$Co(NO_3)_2$ (4.76 mg, 0.016 mmol) in methanol (1 mL) was added to a solution of **2a** (10.0 mg, 0.016mmol) in 1,2-dichloroethane (1 mL). Slow evaporation of the solution afforded a pink crystalline product **2a**/$Co(NO_3)_2$ suitable for X-ray analysis. Mp: 251.0 °C (dec.). Anal. Calcd. For $C_{44}H_{52}CoN_6O_6$: C, 64.46; H, 6.39 ; N, 10.25. Found: C, 64.46; H, 6.35 ; N, 10.32.

Synthesis of 2b/$AgCF_3SO_3$

$AgCF_3SO_3$ (16.3 mg, 0.063 mmol) in methanol (10 mL) was added to a solution of **2b** (51.4 mg, 0.063 mmol) in dichloromethane (10 mL). The colourless precipitate obtained was filtered and dissolved in acetonitrile. Vapor diffusion of methanol into the acetonitrile solution afforded a colourless crystalline product **2b**/$AgCF_3SO_3$ suitable for X-ray analysis. Mp: 98.2-99.0 °C. Anal. Calcd. For $C_{47}H_{51}AgF_7N_5O_3S$: C, 56.07; H, 5.11 ; N, 6.96. Found: C, 56.01; H, 4.97 ; N, 6.95.

Synthesis of 2c/$AgCF_3SO_3$

$AgCF_3SO_3$ (17.5 mg, 0.068 mmol) in methanol (10 mL) was added to a solution of **2c** (49.5 mg, 0.070 mmol) in dichloromethane (10 mL). The colourless precipitate obtained was filtered and dissolved in acetonitrile. Vapor diffusion of methanol into the acetonitrile solution afforded a colourless crystalline product **2c**/$AgCF_3SO_3$ suitable for X-ray analysis. Mp: 140.1 °C (dec.). Anal. Calcd. For $C_{46.8}H_{50.7}AgF_3N_{8.9}O_{11}S$: C, 50.60; H, 4.60 ; N, 11.22. Found: C, 50.22; H, 4.74 ; N, 11.28.

Synthesis of (S)-(+)-3-methylpentanenitrile ((*S*)-G3)[42]

After NaCN (1.02 g, 20.7 mmol) in dry DMSO (6 mL) was stirred for 10 minutes at 82 °C under nitrogen atmosphere, (S)-(+)-1-chloro-2-methylbutane (2.22 g, 20.8 mmol) was dropped and stirred for 19h at 82 °C under nitrogen atmosphere. After cooled until room temperature, water (20 mL) and ether (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (30 mL x 2). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally purified by column chromatography using $CHCl_3$ as solvent. Flash column chromatography afforded the product as a colourless oil in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (dd, *J* = 16.6 Hz, *J* = 5.9 Hz, 1H), 2.25 (dd, *J* = 16.6 Hz, *J* = 6.9 Hz, 1H), 1.78 (oct, *J* = 6.6 Hz, 1H), 1.53 – 1.42 (m, 1H), 1.40 – 1.29 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.0, 32.1, 28.7, 24.1, 19.1, 11.3. $[\alpha]_D^{23}$ +8.79 (*c* 5.11, $CHCl_3$).

Synthesis of (S)-4,8-dimethylnon-7-enenitrile ((*S*)-G4)[43]

After a mixture of (S)-2,6-dimethyl-8-bromo-octane (2.65g, 12.1 mmol) and NaCN (0.67 g, 13.6 mmol) in dry DMSO (20 mL) was stirred for overnight at 50 °C under nitrogen atmosphere. After cooled until room temperature, water and ether was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water, dried over Na_2SO_4. After concentration the crude product was obtained as a yellowish oil in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 – 5.06 (m, 3H), 2.41 – 2.27 (m, 2H), 2.07 – 1.91 (m, 2H), 1.76 – 1.70 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60 – 1.55 (m, 1H), 1.52 – 1.43 (m, 1H), 1.39 – 1.30 (m, 1H), 1.23 – 1.14 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H)). ^{13}C NMR (100 MHz, $CDCl_3$): δ131.6, 124.2, 120.0, 36.4, 32.3, 31.7, 25.7, 25.3, 18.7, 17.7, 14.9. FAB-MS (matrix DTT/TG = 1:1): *m/z* 166 ([M+H]$^+$, 70%). $[\alpha]_D^{20}$ +4.60 (*c* 5.09, $CHCl_3$).

Solvents for CD measurements

Several solvent systems were applied to measure CD spectra. When $CDCl_3$, CD_2Cl_2, 1,2-dichloroethane, EtOAc, mixtures of MeOH and $CHCl_3$, and MeOH and 1,2-dichloroethane were used, seriously noisy CD spectra were obtained. Finally, we found that a mixture of EtOH and dioxane (9:1) shows the best CD spectra.

X-ray crystallographic analysis

All data were collected on a Bruker SMART APEX II ULTRA diffractometer equipped with graphite monochromated Mo K_α radiation (λ = 0.71073 Å) generated by a rotating anode. The cell parameters for the compounds were obtained from a least-squares refinement of the spot. Data collection, data reduction and semi-empirical absorption correction were carried out using the software package of APEX2.[44] All of the calculations for the structure determination were carried out using the SHELXTL package.[45] In all cases, nonhydrogen atoms were refined anisotropically and hydrogen atoms were placed in idealized positions and refined isotropically in a riding manner along with their respective parent atoms. Relevant crystal data collection and refinement data for the crystal structures are summarized in Table S4. CCDC 1974350 (**2a**), 1974351 (**2a**/Ag^+), 1974352 (**2a**/Cd^{2+}), 1974353 (**2a**/Co^{2+}), 1974354 (**2b**/Ag^+) 1974355 (**2c**/Ag^+), 1974357 (**2d**) and 1974358 (**2e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conclusions

The determination of the absolute configurations of several types of chiral nitriles was carried out by measurement of CD spectroscopy of mixtures of chiral nitriles and **2a**/Ag^+. The simple determination system of absolute configuration using the argentivorous molecule is expected to contribute to the research field of determining the absolute configurations of alkyl nitriles with weak optical rotation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Mr Takatoshi Suzuki for the preparation of starting materials. This research was supported by Grants-in-Aid 23550164, 26410100, 17K05844 and 18F18343, from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1 *Triple-Bonded Functional Groups: Supplement C: Part 2*, Vol. 2, ed. A. J. Fatiadi, Wiley-VCH, Weinheim, 1983.
2 Y. Ping, L. Wang, Q. Ding and Y. Penga, *Adv. Synth. Catal.*, 2017, **359**, 3274-3291.
3 G. Yan, Y. Zhang and J. Wang, *Adv. Synth. Catal.*, 2017, **359**, 4068-4105.
4 F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902-7917.
5 S. T. Murphy, H. L. Case, E. Ellsworth, S. Hagen, M. Huband, T. Joannides, C. Limberakis, K. R. Marotti, A. M. Ottolini, M. Rauckhorst, J. Starr, M. Stier, C. Taylor, T. Zhu, A. Blaser, W. A. Denny, G. L. Lu, J. B. Smaill and F. Rivault, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2150-2155.
6 M. Tsukamoto and H. B. Kagan, *Adv. Synth. Catal.*, 2002, **344**, 453-463.
7 M. G. Finn, *Chirality*, 2002, **14**, 534-540.
8 D. Leung, S. O. Kang and E. V. Anslyn, *Chem. Soc. Rev.*, 2012, **41**, 448-479.
9 T. J. Wenzel and J. D. Wilcox, *Chirality*, 2003, **15**, 256-270.
10 S. Nieto, V. M. Lynch, E. V. Anslyn, H. Kim and J. Chin, *J. Am. Chem. Soc.*, 2008, **130**, 9232-9233.
11 G. A. Korbel, G. Lalic and M. D. Shair, *J. Am. Chem. Soc.*, 2001, **123**, 361-362.
12 D. Leung, J. F. Folmer-Andersen, V. M. Lynch and E. V. Anslyn, *J. Am. Chem. Soc.*, 2008, **130**, 12318-12327.
13 D. Leung and E. V. Anslyn, *J. Am. Chem. Soc.*, 2008, **130**, 12328-12333.
14 X. Lu, J. Tang, X. Dang, X. Jing, K. Xu, H. Lia and B. Liang, *RSC Adv.*, 2017, **7**, 13552-13560.
15 M. T. Reetz, M. H. Becker, K. M. Kühling and A. Holzwarth, *Angew. Chem. Int. Ed.*, 1998, ***37***, 2647-2650.
16 J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17-117.
17 L. S. Moon, R. S. Jolly, Y. Kasetti and P. V. Bharatam, *Chem. Commun.*, 2009, 1067-1069.
18 S. Shinoda, *Chem. Soc. Rev.*, 2013, **42**, 1825-1835.
19 R. Ohshima, M. Kitamura, A. Morita, M. Shiro, Y. Yamada, M. Ikekita and E. Kimura, S. *Inorg. Chem.*, 2010, **49**, 888-899.
20 T. Gunnlaugsson and J. P. Leonard, *Chem. Commun.*, 2005, 3114-3131.
21 H. He, K. Zhao, L. Xiao, Y. Zhang, Y. Cheng, S. Wan, S. Chen, L. Zhang, X. Zhou, K. Liu and H. Zhang, *Angew. Chem. Int. Ed.*, 2019, **58**, 1-5.

22 H. Tsukube and S. Shinoda, *Bull. Chem. Soc. Jpn.,* 2004, **77**, 453-461.
23 H. Ito, H. Tsukube and S. Shinoda, *Chem. Commun.,* 2012, **48**, 10954-10956.
24 H. Misaki, H. Miyake, S. Shinoda and H. Tsukube, *Inorg. Chem.*, 2009, **48**, 11921-11928.
25 Y. Habata, M. Ikeda, S. Yamada, H. Takahashi, S. Ueno, T. Suzuki and S. Kuwahara, *Org. Lett.*, 2012, **14**, 4576-4579.
26 Y. Habata, Y. Oyama, M. Ikeda and S. Kuwahara, *Dalton Trans.*, 2013, **42**, 8212-8217.
27 Y. Habata, A. Taniguchi, M. Ikeda, T. Hiraoka, N. Matsuyama, S. Otsuka and S. Kuwahara, *Inorg. Chem.*, 2013, **52**, 2542-2549.
28 Y. Habata, Y. Okeda, M. Ikeda and S. Kuwahara, *Org. Biomol. Chem.*, 2013, **11**, 4265-4270.
29 Y. Habata, J. Kizaki, Y. Hosoi, M. Ikeda and S. Kuwahara, *Dalton Trans.*, 2015, **44**, 1170-1177.
30 M. Ikeda, A. K. Sah, M. Iwase, R. Murashige, S. Kuwahara and Y. Habata, *Supramol. Chem.*, 2017, **29**, 370-377.
31 "Argentivorous" is different from "argentophilic". "Argentophilic" is used in the sense of Ag^{+}–Ag^{+} interactions. For example, H. Schmidbaur and A. Schier, *Angew. Chem. Int. Ed.*, 2015, **54**, 746-784.
32 *Circular dichroic spectroscopy: exciton coupling in organic stereochemistry*, ed. N. Harada and K. Nakanishi, University Science Books, 1983.
33 *Circular Dichroism: Principles and Applications*, ed. N. Berova, K. Nakanishi and R. W. Woody, Wiley-VCH, Weinheim, 2000.
34 J. Burgess and P. J. Steel, *Coord. Chem. Rev.,* 2011, **255**, 2094-2103.
35 M. Nishio, Y. Umezawa, M. Hirota and Y. Takeuchi, *Tetrahedron*, 1995, **51**, 8665-8701.
36 M. Nishio, *CrystEngComm*, 2004, **6**, 130-158.
37 M. Abe, M. Eto, K. Yamaguchi, M. Yamasaki, J. Misaka, Y. Yoshitake, M. Otsuka and K. Harano, *Tetrahedron*, 2012, **68**, 3566-3576.
38 E. Lee, H. Ju, I.-H. Park, J. H. Jung, M. Ikeda, S. Kuwahara, Y. Habata and S. S. Lee, *J. Am. Chem. Soc.*, 2018, **140**, 9669-9677.
39 Y. Cohen, L. Avram and L. Frish, *Angew. Chem. Int. Ed.*, 2005, **44**, 520-554.
40 L. Avram and Y. Cohen, *Chem. Soc. Rev.*, 2015, **44**, 586-602.
41 Y.-T. Chan, X. Li, J. Yu, G. A. Carri, C. N. Moorefield, G. R. Newkome and C. Wesdemiotis, *J. Am. Chem. Soc.*, 2011, **133**, 11967-11976.
42 W. Kirmsc, W. Gruber and J. Ktiis, *Chem. Rer.*, 1973, ***106***, 1376-1383.
43 Y. Nakano, T. Hirose, P. J. M. Stals, E. W. Meijer and A. R. A. Palmans, *Chem. Sci*., 2012, **3**, 148-155.
44 Bruker, *APEX2 Version 2009.1-0 Data collection and Processing Software*, Bruker AXS Inc., Madison, Wisconsin, U.S.A., 2008.
45 G. M. Sheldrick, *Acta Cryst.,* 2015, **C71**, 3–8.

Graphical abstract

Inclusion of alkyl nitriles by tetra-armed cyclen with styrylmethyl groups

Huiyeong Ju,[a] Honoka Tenma,[a] Miki Iwase,[a] Eunji Lee,[a] Mari Ikeda,[c] Shunsuke Kuwahara[ab] and Yoichi Habata*[ab]

A new technique for assignment of absolute configuration for low $[\alpha]_D$ alkyl-nitriles using Ag^+ complex with tetra-armed cyclen is reported.