Catalytic Asymmetric Synthesis of 2,6-Disubstituted Cuneanes via Enantioselective Constitutional Isomerization of 1,4-Disubstituted Cubanes

Hiyori Takebe, and Seijiro Matsubara*

B.S. H. Takebe, Prof. Dr. S. Matsubara
Department of Material Chemistry,
Graduate School of Engineering, Kyoto University
Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510, Japan
E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp, https://smatsubara.wixsite.com/matsubara-kyoto-u

Supporting information for this article is given via a link at the end of the document.

Abstract: 2,6-Disubstituted cuneane has potential as a *p*-disubstituted benzene bioisostere and a novel chiral scaffold. It is a constitutional isomer of a 1,4-disubstituted cubane obtained via a metal-catalyzed skeletal rearrangement. Unlike the highly symmetrical 1,4-disubstituted cubane, the isomerized 2,6-disubstituted cuneane is a chiral molecule possessing C_2 symmetry. Examining various chiral catalysts revealed that the Pd-pincer catalyst provides a good asymmetric induction.

Introduction

Cubane is the smallest hydrocarbon skeleton that can have substituents in eight directions. Eaton reported the first practical cubane synthesis in 1964.[1][2] The unique hydrocarbon molecule has a width similar to that of benzene. Consequently, it has been introduced into various bioactive compounds as a benzene bioisostere to alleviate hydrophobic interactions and tolerate metabolism.[3] Many researchers, led by Eaton, have developed diversified reactions to introduce or remove substituents on the cubane skeleton, realizing various multi-substituted derivatives. Currently, not only the *p*-substituted benzene bioisostere but also the *o, m*-substituted benzene bioisostere can be developed starting from commercially available dimethyl cubane-1,4-dicarboxylate.[2]-[4] In the case of tri-substituted ones, the cubane skeleton itself has a chance of possessing chirality.[5][6] Although it is unnecessary to impart chirality from the viewpoint of the benzene bioisostere, it does offer a novel chiral scaffold. However, introducing three substituents site-selectively is labor intensive.[7] To date, an asymmetric induction reaction has yet to be reported. Thermally stable regular hexahedral cubane begins to decompose when the temperature exceeds 230 °C. and undergoes skeletal isomerization and finally becomes cyclooctatetraene.[8] During this decomposition process, cubane is sequentially isomerized into various fused cyclic polyhedral hydrocarbons. The first constitutional isomerized product, cuneane, is a stable and isolable cage-like hexahedral hydrocarbon with 3-membered (x 2), 4-membered (x 2), and 5-membered rings (x 2).[9] Eaton also reported that cuneanes are obtained by isomerization of cubanes with Ag(I) or Pd(II) salt.[10] Despite this very interesting structure, cuneanes have not been given much consideration.[11]

Results and Discussion

Due to the size of the molecular skeleton, cuneanes also qualify as benzene bioisosteres. The starting material, 1,4-disubstituted cubane, is achiral, but a C_2 symmetrical 2,6-disubstituted cuneane derivative can be a chiral molecule. According to Eaton's first report,[10] cubanes, which have electron-withdrawing substituents such as an ester group at the 1,4-position, can predominantly give the corresponding chiral 2,6-disubstituted cuneane with a small amount of the 1,3-disubstituted isomer is produced (Figure 1).
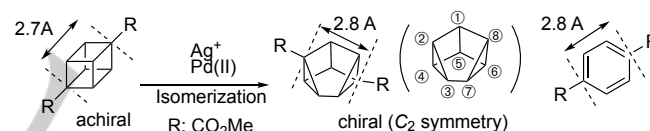

Figure 1. Constitutional Isomerization of Achiral 1,4-Cubanes to Chiral 2,6-Cuneanes. Preparation of "Chiral" Benzene Bioisosteres.

We reexamined the isomerization of dimethyl cubane-1,4-dicarboxylate (**1a**) using Ag, Pd, and Au catalysts as shown in Table 1. In these cases, dimethyl cuneane-2,6-dicarboxylate (**2a**) tends to be the major product. Especially, treatment of **1a** with 5.0 mol% of AgOTf in 1,2-dichloroethane gave **2a** selectively (entry 2). As reported previously,[10] Ag(I) or Pd(II) salt showed catalytic activity, but the catalytic ability of palladium(II) salt was not as high at 80 °C as expected. Au(I) complex has been expected to promote the reaction considering its high activity for σ−π isomerization reaction,[12] and showed a certain level of catalytic activity. Among them, AgOTf, which had the highest activity and selectivity was examined to the isomerization of other 1,4-cubane derivatives (Scheme 1). The reactions shown in Scheme 1 gave the corresponding 2,6-disubstituted racemic cuneanes including iodo-substituted ones.

**Table 1.** Isomerization of Dimethyl Cubane-1,4-dicarboxylate (**1a**).[a]

entry	Cat / mol %	Solvent	T/°C	t /h	2a/%	3a/%	1a/%[b]
1	AgOTf / 50	PhCH₃	100	20	99	<1	<1
2	AgOTf / 5.0	DCE[c]	80	20	96	<1	<1
3	AgOTf / 5.0	DCM[d]	80	20	69	<1	30
4	AgPF₆ / 5.0	DCE	60	20	48	6	14
5	AgSbF₆ / 5.0	DCE	80	20	46	8	31
6	Pd(OAc)₂ / 5.0	DCE	80	20	3	<1	22
7	Pd(TFA)₂ / 5.0	DCE	80	20	3	4	8
8	PdCl₂(MeCN) / 5.0	DCE	80	20	25	4	25
9	(AuPPh₃)OTf / 5.0	DCM	20	4	9	<1	33
10	(AuPPh₃)OTf / 5.0	DCM	60	20	48	6	10
11	(AuPPh₃)OTf / 5.0	DCE	80	20	21	4	76

[a] **1** (0.3 mmol), solvent (3 ml), under Ar. [b] Recoveries. [c] DCE: 1,2-dichloroethane, [d]DCM: dichloromethane.
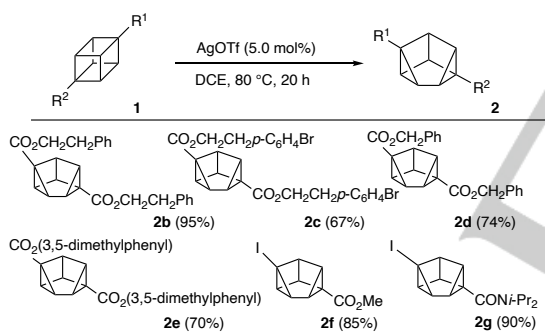

Scheme.1. Ag⁺-catalyzed Constitutional Isomerization of 1,4-Cubanes to 2,6-Cuneanes

The chiral resolution of diester **2b** using chiral HPLC was examined. Both enantiomers are separable. The isolated enantiomers show the reversal of optical rotations (Fig. 2). Based on the DFT-calculated ECD spectra for the preferable conformers, the **P**-isomer of **2b** should have a negative [α] value.[13] For the assignment of the absolute configuration of the 2,6-disubstituted cuneanes **2b**, we followed the rule for axially chiral molecules. Accordingly, it was viewed from an angle with respect to the main axis (③ − ⑦), where the chirality can be set. The **P** isomer denotes the clockwise placement of the near and far substituents, while **M** indicates a counterclockwise placement.

Eaton reported that the mechanism of the isomerization involves a cationic intermediate, which is formed by the interaction of Ag⁺ with strained σ-bond of cubane.[10][14] The detailed mechanism was not shown, but the use of Ag(I) or Pd(II) with a chiral ligand may result in asymmetric induction. Figure 3 shows the schematic
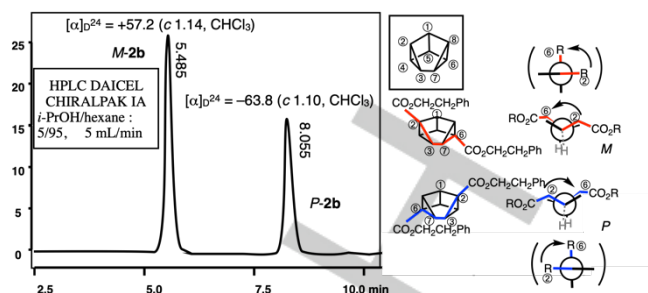
Figure 2. cHPLC Separation of Enantiomers of Chiral Cuneane **(+)-2b/(–)-2b**; assignment of the stereochemical description (Absolute configuration of each enantiomer is based on ref 13).

analysis of the isomerization from 1,4-cubane into 2,6-cuneane. In the 1,4-disubstituted cubane, whose substituents on ① and ④ are electron-withdrawing such as ester, Lewis acidic catalyst will not interact with the electron-deficient bonds (black), but does preferentially with bonds a-f (red and green). For isomerization into cuneanes, two C–C bonds in cubanes should be cleaved and recombined. In addition, these two bonds should be skew. When the two skew red bonds participate in the reaction in Figure 3 (*ie*, a-c, a-e, or c-e), the product will be the **P**-isomer, whereas the reaction of the two skew green bonds (*ie*, b-d, b-f, or d-f), will give the **M**-isomer. For asymmetric induction, the catalyst must perform the very difficult task of choosing three of the six alternating arrangements around the 1,4-axis of cubane as it approaches.
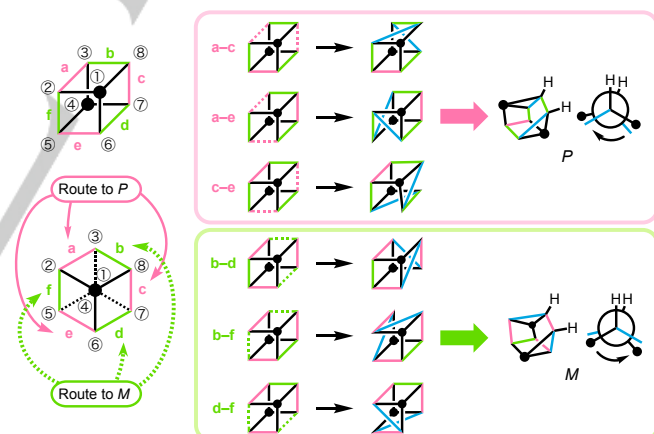
Figure 3. Schematic Explanation for the Asymmetric Isomerization.

If the reaction proceeds via a cationic intermediate as formerly suggested, the use of Ag⁺ accompanying an optically active anion such as BINAPHOS may show some asymmetric induction. Various chiral catalysts of Ag⁺-chiral phosphate were examined,[15] but a positive result is not obtained (Table 2, entries 1–5). Employing specific Pd catalysts may change the reaction mechanism. If a Pd-coordinated intermediate is formed, cubane would be diastereomers **A** and **B**. If one matched diastereomer (**A**) isomerizes to the cuneane faster than the other **B**, the product will display optical activity (Figure 4). The mismatched **B** would be converted into the matched one (**A**) via starting material under equilibrium. The back-donation character of Pd metal may provide enough stabilization for the equilibrium between diastereomers.
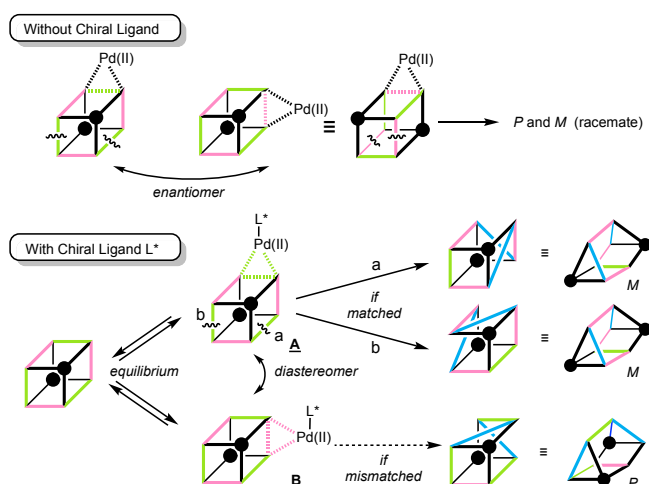
Figure 4. Working-hypothesis for Asymmetric Induction via Palladacycle

We then examined a series of Pd catalysts. Pd(II) salts are not active enough for the rearrangement (Table 1), so, a cationic Pd(II) species formed by treatment of Pd–X with AgOTf was also examined. The catalyst prepared from BINAP-PdCl$_2$/AgOTf via an asymmetric C-C bond–forming reaction as reported by Mikami and Sodeoka [16] did not work well (entry 6) in this case. A cationic Pd(II) with a chiral pincer ligand was investigated (entries 8, 10–11). The N–C–N pincer ligand was not active for isomerization (entry 8). However, the P–C–P ligand gave **2** with a reasonable asymmetric induction (entry 10). Using the enantiomer of the ligand showed the opposite asymmetric induction (entry 11).[17] Entries 12–15 show the results of tuning the ester group in **1**.
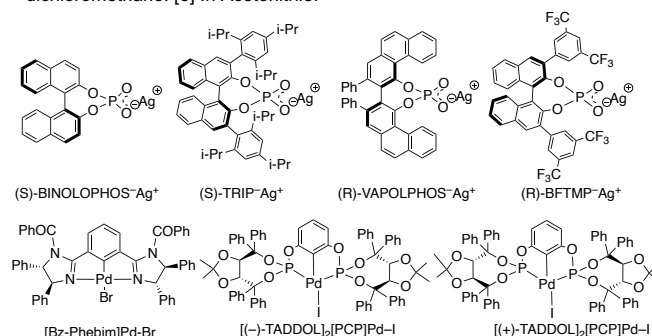
Conclusion

The highly symmetric regular hexahedral hydrocarbon first reported in 1964 can be converted into an optically active cage-like hexahedral hydrocarbon cuneane in one step, although the yield and ee in this study were not always sufficient. The racemic isomerization reaction was demonstrated in 1970, and this study is the first to report the development of the asymmetric version. It is interesting that the isomerization of cubic molecules with a very high symmetry induces asymmetry at the rigid reaction site of the chiral Pd-pincer catalyst. This approach should be applicable to similar isomerization reactions. This study focuses on the asymmetric synthesis of the major product, 2,6-disubstituted cuneanes; however, 1,3-disubstituted cuneanes, which are produced as a by-product, are also chiral molecules. In the future, we plan to expand the range of disubstituted cuneanes that can be asymmetrically synthesized as well as 1,3-disubstituted ones from achiral cubanes. The asymmetric synthesis of these chiral cage-shaped polyhedral hydrocarbons indicates the emergence of new chiral scaffolds.

Table 2. Asymmetric Isomerization of Cubane-1,4-dicarboxylic acid ester (**1**) into Cuneane-2,6-dicarboxylic acid ester (**2**).[a]

entry	Catalyst / Temp °C/ time h	R in **1**	**2**/%	% ee	[α]$_D^{20}$	**1**/%
1	(S)-BINAP / AgOTf (10 mol%) /80 °C /20 h	CH$_2$CH$_2$Ph (**1b**)	<1 (**2b**)	NA	NA	89
2	(S)-BINOLPHOS⁻Ag⁺ (10 mol%) /80 °C /24 h	**1b**	20 (**2b**)	2	NA	38
3	(S)-TRIP⁻Ag⁺ (15 mol%) /80 °C /84 h	**1b**	15 (**2b**)	10	NA	81
4	(R)-VAPOLPHOS⁻Ag⁺ (15 mol%) /80 °C /72 h	**1b**	30 (**2b**)	2	NA	65
5	(R)-BFTMP⁻Ag⁺ (15 mol%) /80 °C /72 h	**1b**	<1 (**2b**)	NA	NA	<1
6	[(+)-BINAP]$_2$PdCl$_2$ / AgOTf (5 mol%) /80 °C/ 20 h	**1b**	<1 (**2b**)	–	NA	>90
7	[Bz-Phebim]Pd-Br (5 mol%) /80 °C /20 h	**1b**	<1 (**2b**)	–	NA	>90
8	[Bz-Phebim]Pd-Br / AgOTf (5 mol%) /80 °C /20 h	**1b**	<1 (**2b**)	–	NA	>90
9	[(–)-TADDOL]$_2$[PCP]Pd–I (5 mol%) /80 °C /20 h	**1b**	<1 (**2b**)	NA	NA	>90
10	[(–)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /72 h	**1b**[c]	31 (**2b**)	67	+42.7 (c 1.03)[d]	39
11	[(+)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /72 h	**1b**[c]	52 (**2b**)	–55	–39.0 (c 1.05)[d]	15
12	[(–)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /72 h	CH$_2$CH$_2$pC$_6$H$_4$Br (**1c**)	23 (**2c**)	78	+41.7 (c 0.79)[e]	40
13	[(+)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /72 h	**1c**	41 (**2c**)	–52	–20.2 (c 0.79)[e]	30
14	[(–)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /60 h	CH$_2$CH$_2$pC$_6$H$_4$F (**1h**)	28 (**2h**)	62	+17.1 (c 0.85)[e]	32
15	[(–)-TADDOL]$_2$[PCP]Pd–I / AgOTf (5 mol%) /50 °C /60 h	CH$_2$CH$_2$pC$_6$H$_4$Cl (**1i**)	40 (**2i**)	63	+2.4 (c 0.82)[e]	21

[a] **1** (0.3 mmol), solvent (3 ml), under Ar. DCE: 1,2-dichloroethane. According to the calculation of ref 13, [b] 1,3-Isomers were also observed; see SI. [c] As a result of DFT-calculation, the major enantiomer of entry 10 was *M*-isomer; that of entry 11 was *P*-isomer. See ref 13. [d] In dichloromethane. [e] In Acetonitrile.

(S)-BINOLOPHOS⁻Ag⁺   (S)-TRIP⁻Ag⁺   (R)-VAPOLPHOS⁻Ag⁺   (R)-BFTMP⁻Ag⁺

[Bz-Phebim]Pd-Br   [(–)-TADDOL]$_2$[PCP]Pd–I   [(+)-TADDOL]$_2$[PCP]Pd–I

Experimental Section

Preparation of 1,4-Cubanedicarboxylic acid ester as starting material (1b-e, 1h-i)

A mixture of 1,4-cubanedicarboxylic acid (2.0 mmol) and thionyl chloride (4.0 mL) was heated and stirred under reflux for 3 h in Ar.

The excess thionyl chloride was removed by short-path distillation and volatiles were completely removed under vacuum at rt for 30 min. To the residue, dichloromethane (DCM, 5.0 mL) was added. The resulting solution was cooled to 0 °C under Ar. To the cooled solution, a solution of alcohol (4.4 mmol) and Et₃N (6.0 mmol) in DCM (4.0 mL) was added dropwise at 0 °C under Ar, followed by an addition of a catalytic amount of DMAP. The mixture was stirred for 15 min at 0 ℃, and then warmed to rt over 12 h. About 20mL of DCM was added to the mixture, and the organic layer was washed with HCl (1.0 M). After extracting the aqueous solution with DCM, the organic layer is washed lightly with brine (10 mL). The combined organic layers were concentrated under vacuum. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/4) as eluent. The title compound was isolated.

Reaction of cubane-1.4-dicarboxylic acid ester with [(–)-TADDOL]₂[PCP]Pd–I / AgOTf (Table2, entries 10,12,14, and 15)

[(–)-TADDOL]₂[PCP]Pd–I was prepared followed by the procedure of Szabó.[17b] AgOTf (0.015 mmol, 3.8 mg) and [(–)-TADDOL]₂[PCP]Pd–I (0.02 mmol, 26 mg) were dissolved to dichloroethane (3.0 mL) under Ar atmosphere and stirred for 10 min at room temperature. Then, 1,4-cubanedicarboxylate (0.30 mmol) in dichloroethane (3.0 mL) was added to this mixture and stirred at the indicated temperature in Table 2. After stirred for the period shown in Table 2, the resulting mixture was passed through a short silica-gel column, concentrated under vacuum and purified on silica-gel using ethyl acetate/hexane (1/4) as eluent. After purification, the ee of the product was measured by cHPLC (DAICEL CHIRALPAK IA i-PrOH/Hexane: 5/95).

Acknowledgements

Keywords: Asymmetric Synthesis • Chiral Scaffold• Cubane • Cuneane • Pd-pincer

[1] P. E. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, *86*, 962-964.

[2] a) P. E. Eaton, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1421-1436; b) K. F. Biegasiewicz, J. R. Griffiths, G. P. Savage, J. Tsanaktsidis, R. Priefer, *Chem. Rev.* **2015**, *115*, 6719-6745.

[3] a) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage, C. M. Williams, *Angew. Chem. Int. Ed.* **2016**, *55*, 3580-3585; b) S. D. Houston, T. Fahrenhorst-Jones, H. Xing, B. A. Chalmers, M. L. Sykes, J. E. Stok, C. F. Soto, J. D. Burns, P. V. Bernhardt, J. J. De Voss, G. M. Boyle, M. T. Smith, J. Tsanaktsidis, G. P. Savage, V. M. Avery, C. M.Williams, *Org. Biomol. Chem.* **2019**, *17*, 6790-6798; c) K. J. Flanagan, S. S. R. Bernhard, S. Plunkett, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 6941-6954.

[4] N. Grover, M. O. Senge, *Synthesis* **2020**, *52*, 3295-3325.

[5] a) P. E. Eaton, Y. Xiong, C.-H. Lee, *J. Chin. Chem. Soc. (Taipei)*, **1991**, *38*, 303-306; b) R. Okude, G. Mori, A. Yagi, K. Itami, *Chem. Sci.* **2020**, *11*, 7672–7675; c) A. A. Fokin, P. R. Schreiner, R. Berger, G. H. Robinson, P. Wei, C. F. Campana, *J. Am. Chem. Soc.* **2006**, *128*, 5332-5333.

[6] a) N. Yoshino, Y. Kato, T. Mabit, Y. Nagata, C. M. Williams, M. Harada, A. Muranaka, M. Uchiyama, S. Matsubara, *Org. Lett.* **2020**, *22*, 4083–4087; b) Y. Kato, C. M. Williams, M. Uchiyama, S. Matsubara, *Org. Lett.* **2019**, *21*, 473-475.

[7] N. Yoshino, Y. Kato, Y. Shimada, C. M. Williams, S. Matsubara, *Isr. J. Chem.* **2021**, *61*, 380-386.

[8] a) K. Hasseurück, H.-D. Martin, R. Walsh, *Chem. Ber.* **1988**, *121*, 369-372. b) H. Xing, S. D. Houston, X. Chen, S. Ghassabian, T. Fahrenhorst-Jones, A.Kuo, C.-E. P. Murray, K.-A. Conn, K. N. Jaeschke, D.-Y. Jin, C. Pasay, P. V. Bernhardt, J. M. Burns, J. Tsanaktsidis, G. P. Savage, G. M. Boyle, J. J. De Voss, J. McCarthy, G. H. Walter, T. H. J. Burne, M. T. Smith, J.-K. Tie, and C. M. Williams, *Chem. Eur. J.* **2019**, 2729-2734.

[9] M. V. Roux, J. Z. Dávalos, P. Jiménez, R. Notario, O. Castaño, J. S. Chickos, W. Hanshaw, H. Zhao, N. Rath, J. F. Liebman, B. S. Farivar, A. Bashir-Hashemi, *J. Org. Chem.* **2005**, *70*, 5461-5470.

[10] L. Cassar, P. E. Eaton, J. Halpern, *J. Am. Chem. Soc.* **1970**, *92*, 6366-6368.

[11] a) S. Moss, B. T. King, A. de Meijere, S. I. Kozhushkov, P. E. Eaton, J. Michl. *Org. Lett.* **2001**, *3*, 2375-2377; b) J.-J. M. Abboud, I. A. Koppel, J. Z. Dávalos, P. Burk, I. Koppel, E. Quintanilla, *Angew. Chem. Int. Ed.* **2003**, *42*, 1044-1046; c) G. Durkó, I. Jalsovszky, *Tetrahedron* **2013**, *69*, 5160-5163.

[12] D. Hack, M. Blümel, P. Chauhan, A. R. Philipps, S. Enders, *Chem. Soc. Rev.* **2015**, *44*, 6059-6093.

[13] H. Takebe, A. Muranaka, M. Uchiyama, S. Matsubara, *Chem. Lett.* **2022,** *51*, doi.org/10.1246/cl.220197

[14] J. E. Byrd, L. Cassar, P. E. Eaton, J. Halpern, *J. Chem. Soc. D* **1971**, 40-41.

[15] a) L. Yang, R. Melot, M. Neuburger, O. Baudoin, *Chem. Sci.* **2017**, *8*, 1344-1349; b) A. P. Smalley, J. D. Cuthbertson, M. J. Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412-1415; c) J. Luo, T. Zhang, L. Wang, G. Liao, Q.-J. Yao, Y.-J. Wu, B.-B. Zhan, Y. Lan, X.-F. Lin, B.-F. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 6708-6712; d) C.-C. Tsai, C. Sandford, T. Wu, B. Chen, M.-S. Sigman, F. D. Toste, *Angew. Chem. Int. Ed.* **2020**, *59*, 14647-14655.

[16] a) M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648-2649; b) K. Aikawa, Y. Hioki, N. Shimizu, K. Mikami, *J. Am. Chem. Soc.* **2011**, *133*, 20092-20095.

[17] a) J.-K. Liu, J.-F. Gong, M.-P. Song, *Org. Biomol. Chem.* **2019**, *17*, 6069-6098; b) O. A. Wallner, V. J. Olsson, L. Eriksson, K. J. Szabó, *Inorg. Chem. Acta* **2006**, *359*, 1767-1772.

Entry for the Table of Contents
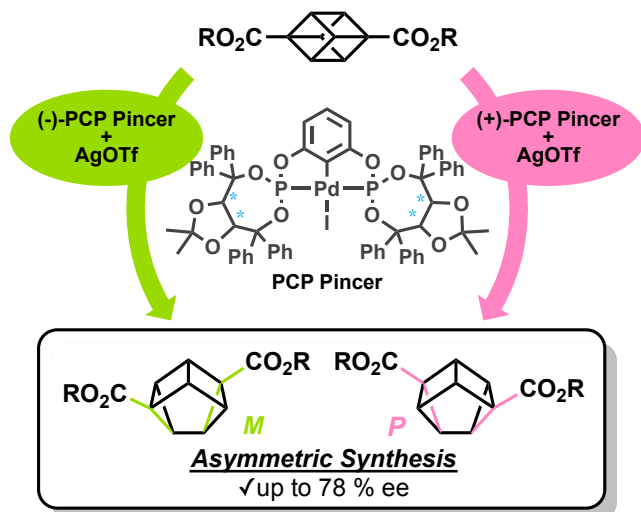
2,6-Substituted cuneanes, obtained by metal-catalyzed isomerization of 1,4-disubstituted cubanes, are the stable cage-like hexahedral hydrocarbon with chirality (C_{2v} symmetry). In this process, the chiral cage-like hexahedral hydrocarbon in one step. The asymmetric induction was performed using chiral P–C–P pincer Pd catalyst. The obtained cuneane will be a novel chiral scaffold.