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How to Set the "Chirality" of Polyhedral Small Molecule Hydrocarbons: Decoration and Editing of Cubane Skeleton

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Dedicated with deep respect to Professor Eaton, who bestowed upon us dream molecules like cubanes and cuneanes, and who is no longer with us.

Small polyhedral hydrocarbons represented by cubane have attracted attention as potential molecular scaffolds for pharmaceuticals as benzene bioisoster. Cubane is also expected to be used as a chiral scaffold, but due to its high symmetry, it is necessary to introduce chirality by sequential site-selective introduction of substituents. Furthermore, polyhedral desymmetrized isomers of cubane, such as cuneane and semibullvalene, and extended cage compounds, such as bishomocubane and homocuneane, exhibit chirality and are also expected to be used as new optically active scaffolds. In this concept, we would like to explain the synthetic routes we have planned, specifically, the decoration and editing of the cubane skeleton.

1. Introduction

The cubic hydrocarbon, cubane, represented by the molecular formula C_8H_8, is a saturated hydrocarbon synthesized by Prof. Eaton in 1964. It unveiled a molecular shape and properties inconceivable by conventional knowledge of saturated hydrocarbons composed from tetrahedral sp^3 carbon units.[1,2] Despite its significant strain, the cubane framework is thermally stable. Its ability to generate active species such as anions, radicals, and cations, coupled with its amenability to various modification reactions, suggests its potential for incorporation it as a substructure into diverse bioactive organic molecules.[3] Due to these characteristics, the synthesis of novel compounds and drug candidates based on cubane is feasible, paving the way for a captivating area within organic synthetic chemistry. We anticipated that inducing chirality in cage hydrocarbons, represented by cubane, and using these molecules as new small molecular scaffolds, would be an extremely attractive field of research.

When viewed vertex-to-vertex, cubane projects as a hexagon, evoking the shape of benzene. The inter-vertex molecular width nearly matches that of benzene (ca 2.7 Å), and given the congruence in the formula $(CH)_n$, cubane has been anticipated as a benzene bioisostere.[4] Based on this concept, attempts have been made to replace the benzene ring in various bioactive molecules with cubane to improve biological activity. Such attempts can be traced back to the evolution of diversity-oriented synthesis (DOS) over the past few decades, which gave rise to various strategies to enhance the diversity and complexity of pharmaceutically relevant molecules. Increasing the number of quaternary carbon centers in medicinal and agrochemical molecules enhances the steric complexity of potential drug candidates, offering an effective means to "escape from flatland", as suggested by Lovering.[5] In this sense, units like cubane, which have the same molecular width as benzene but only contain tertiary carbons, can be deemed ideal hydrocarbon units. Moreover, cubane not only serves as a simple benzene bioisostere, but its three-dimensional unit itself can express chirality. As a highly bridged saturated hydrocarbon, cubane possesses a rigid three-dimensional structure that remains undeformed. Therefore, it's feasible to induce a robust chiral center in cubane by site-selectively introducing substituents (Figure 1, red). However, given its highly symmetrical (O_h symmetry) structure, creating a chiral environment on the cubane skeleton remains a challenging endeavour. Motivated

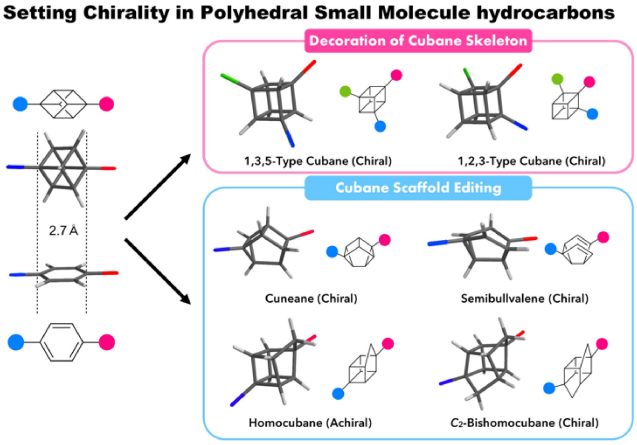

Figure 1. Two strategies to set chirality in cubane derivatives: Decoration on cubane (red) and cubane scaffold editing (blue).

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by this intriguing aspect, we have been examining the conferral of chirality onto the cubane skeleton.[6,7] Due to its high symmetry, at least three substituents must be introduced for cubane to express chirality, and these three must be site-selectively introduced.[3,6a,8] As discussed in later chapters, site-selective substituent introduction on the highly symmetrical cubane remains a challenging synthetic chemistry problem yet to be fully resolved.[3] Beyond these selective organic synthesis efforts, we have conceived a highly efficient idea. Namely, could the constitutional isomerization of the cubane skeleton also lead to the construction of chiral molecules, rather than traditional substitution reactions? Inspired by terms such as "molecular editing" and "scaffold hopping",[9] we have named this "cubane scaffold editing" and decided to investigate it. In fact, half a century ago, in 1970, Eaton reported that when catalysts such as Ag(I) or Pd(II) act on cubane, it transforms into a twisted new hexahedral molecule called cuneane.[10] Commercially available dimethyl 1,4-cubanedicarboxylate demonstrates its conversion into dimethyl 2,6-cuneanedicarboxylate, while 1,4-bis(acetoxymethyl)cubane shows it transforms into a 1,3-disubstituted form. As cuneane is a C_{2v} symmetric molecule, even mono and di-substituted forms can express chirality. Thus, with a single reaction operation of isomerization, cuneane can impart complexity, like chirality, to the molecule without significantly altering its size from cubane.[11] Additionally, introducing two methylene groups into two of the eight equivalent bonds of the cubane skeleton can lead to bishomocubane, which can also possess chirality (Figure 1, blue).[12] Using molecules like cuneane and bishomocubane represents a novel strategy of conferring chirality not by "decoration" of the cubane skeleton's vertices but by altering the molecular shape, i.e., "cubane scaffold editing". We believe that if we can impart complexity, such as chirality, to a molecule with a highly symmetrical three-dimensional framework like cubane by means of "disrupting" its symmetry through scaffold editing, then access to optically active cage-type polyhedral molecule, which have so far been deemed challenging to synthesize, becomes feasible. In this Concept, we introduce chirality via substituent introduction to cubane and discuss the synthesis associated with imparting chirality to polyhedral hydrocarbons like cuneane, semibullvalene, and bishomocubane, thereby highlighting the future possibilities in this field of research.

2. Decoration of Cubane Skeleton

Cubane is the smallest hydrocarbon skeleton that can have substituents in eight directions. Eaton reported the first practical cubane synthesis in 1964.[1] Many researchers, led by Eaton, have developed diversified reactions to introduce or remove substituents on the cubane skeleton, realizing various multi-substituted derivatives.[2,3,13] When possessing at least three or more substituents, the cubane skeleton itself has the potential to exhibit chirality.[3,6–8] It is possible to repeat the DoM (Directing *ortho*-Metalation) process twice to synthesize 1,2,3-trisubstituted cubanes; 1,2,3-trisubstituted cubane can be chiral molecule. The chiral cubanes, **2a**,[8a] **4**,[8b] and **7**[6a] in Scheme 1 were prepared and **4** and **7** were resolved by chiral high-performance liquid chromatography (cHPLC). The specific rotation of **7** was also shown by Yoshino and Matsubara (Scheme 1).[6a]

Takebe and Matsubara selected bis(*(R)*-cyclohexyl)amine, which was previously used by Anderson for the stereoselective deprotonation of bicyclo[1.1.1]pentane derivative,[14,15] and performed DoM on disubstituted cubane **8**. Carboxylic acids **9a** and **9b** were isolated at 70% and 16% respectively (63% de). This reaction represents the first example of asymmetric synthesis of 1,2,3-trisubstituted cubane (Scheme 2).[16]

A trisubstituted cubane with substituents at the 1,3,5-positions also becomes chiral if the three substituents are different. Kato and Matsubara showed a solution by demonstrating the preparation of chiral 1,3,5-trisubstituted cubane starting from the achiral compound **10** (Scheme 3). Treatment of **10** with nBu$_4$ZnLi$_2$ led to the elimination of two bromine atoms, forming 1,3-cubene **11** with a charge-shift bond (CSB).[6b,7] This reactive bond can react with a carbanion equivalent to afford *n*-butylated cubyl zinc species, which can be quenched with electrophiles.

3. Cubane Scaffold Editing

As shown in Section 2, in order to introduce an asymmetric environment into a highly symmetric 1,4-disubstituted cubane, it is necessary to selectively introduce two additional substituents that solely serve the role of asymmetric induction. Frankly speaking, it must be said that using cubane as a chiral scaffold is not a very smart approach. For these reasons, the "Cubane

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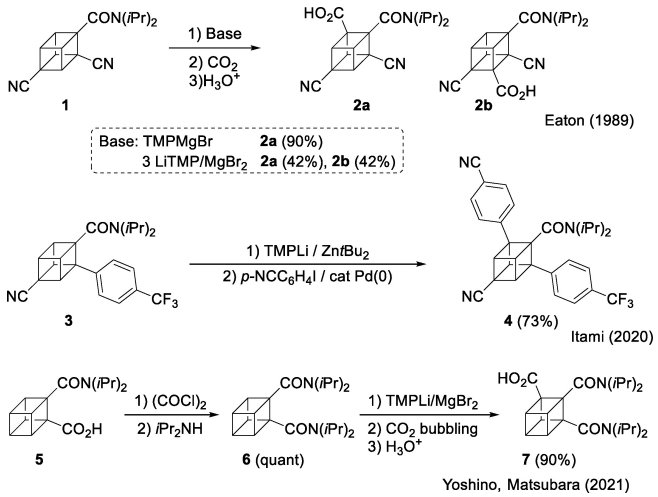
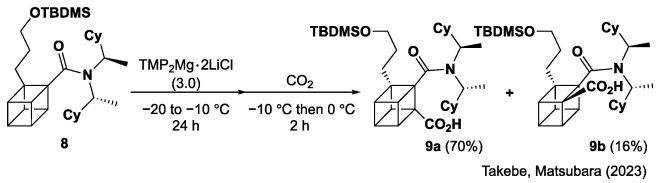
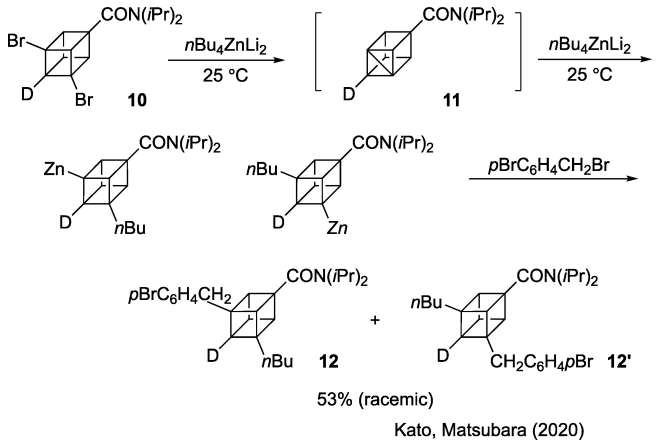
Seijiro Matsubara was educated in chemistry at Kyoto University, completing his PhD in 1986 with Professors Hitosi Nozaki and Kiitiro Utimoto, and at the Université de Lausanne (1984–1985) where he was a PhD course student with Prof. Manfred Schlosser. He was appointed as an Assistant Professor at Kyoto University in 1986. After postdoctoral research with Prof. Barry M. Trost at Stanford University in 1988–1989, he became an Associate Professor at Kyoto University in 1995. In 2006, he became a Full Professor at Kyoto University.



Scheme 1. Preparation of 1,2,3-trisubstituted cubanes.

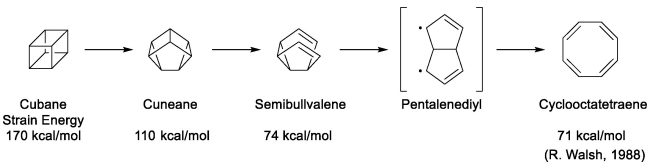


Scheme 2. Chiral auxiliary induced asymmetric synthesis of 1,2,3-trisubstituted cubane.



Scheme 3. Preparation of 1,3,5-trisubstituted cubane as a racemic mixture (**12** and **12'**).

Scaffold Editing" technique mentioned in Section 1 is anticipated to be more practical. As shown in Fig 1, there are two types of deformation of the cubane skeleton: constitutional isomerization and expansion through methylene insertion. The former is based on the thermal isomerization reaction of cubane. Thermally stable regular hexahedral cubane begins to decompose when the temperature exceeds 230 °C and undergoes skeletal isomerization and finally becomes cyclooctatetraene (Scheme 4).[17] The idea is to utilize several types of cage molecules that are produced along this pathway. The latter is a type of cage expansion, which proceeds by generating cation



Scheme 4. Thermal decomposition route from cubanes with strain releasing.

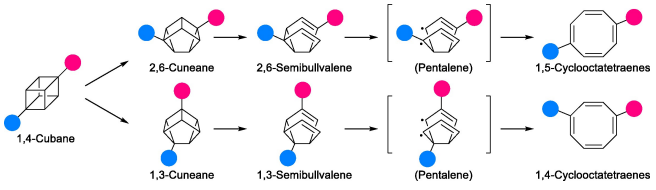
equivalents on the carbon adjacent to the cage. For example, a molecule in which a single methylene group has been inserted into cubane is called homocubane.

It has been shown that 2,6- and 1,3-disubstituted cubanes can be selectively obtained from commercially available 1,4-disubstituted cubanes (details are provided in Section 3.1). Advancing the isomerization of these cuneanes leads to the formation of 2,6- and 1,3-semibullvalenes, respectively, and it is considered that they eventually become 2,6- and 1,3-disubstituted cyclooctatetraenes. These cuneanes and semibullvalenes are chiral molecules. It is important to note that the disubstituted semibullvalenes obtained by isomerization from cuneanes retain the stereochemistry of the original cuneanes. The asymmetric induction in the formation of disubstituted cuneanes from achiral 1,4-disubstituted cubanes is crucial for "Scaffold Editing" (Scheme 5).

3.1. Cuneane

As described above, during the strain releasing process, cubane isomerizes into cuneane first. The O_h symmetry of cubane is reduced to C_{2v} when it becomes cuneane. Therefore, even a mono-substituted body exhibits chirality. Cuneane can also be a chiral molecule with a single substituent. As shown in the Figure 2a and 2b, the mono-substituted cuneanes at ②, ④, ⑥, or ⑧ positions have chirality, and in the disubstituted case, there are seven different types of chiral cuneanes. In the case of 2,4-disubstituted, different types of substituents are required.

Since Eaton's synthesis in 1964,[1] the most readily available cubane derivative has been dimethyl 1,4-cubanedicarboxylic acid, which is commercially available. In the isomerization reaction from 1,4-substituted derivatives to cuneane, significant selectivity is observed depending on the electronic properties of the substituents. According to Eaton's first report in 1970,[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 as a major product, whereas if these substituents are acyloxymethyl



Scheme 5. Scaffold editing starting from 1,4-disubstituted cubane.

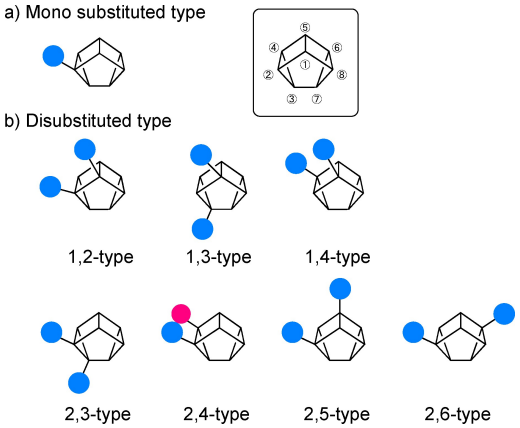
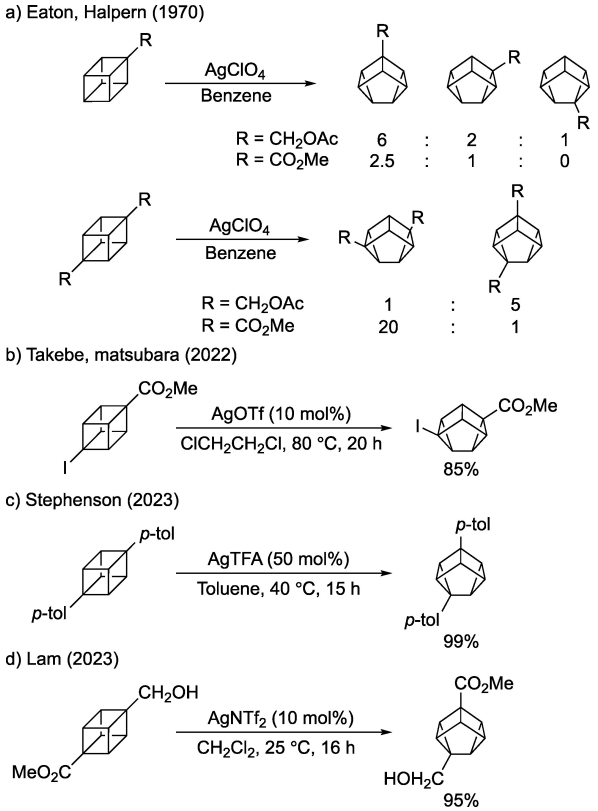


Figure 2. Chiral cuneanes: a) Monosubstituted type: b) Disubstituted type.

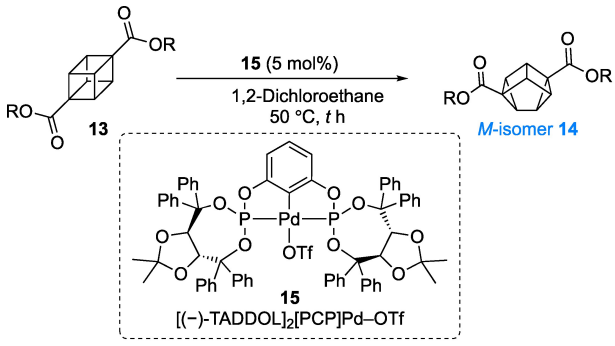
groups, it becomes 1,3-disubstituted one (Scheme 6a). The isomerization was well examined recently to clear the tendency of selectivity depends on the substituents (Scheme 6b,[11a] 6c,[18a] 6d[18b]).

In 2022, Takebe and Matsubara succeeded in the asymmetric synthesis of 2,6-cuneanedicarboxyllic acid diesters from 1,4-cubanedicarboxylic acid diesters (Table 1).[11a] Examining various chiral catalysts revealed that the Pd-pincer catalyst provides a good asymmetric induction. Determination of the absolute configuration of each enantiomer was performed based on ECD (Electronic Circular Dichroism) spectra and DFT calculation.[11b]



Scheme 6. Isomerization of cubanes to cuneanes by Ag(I) catalyst.

Table 1. . Catalytic asymmetric isomerization from cubane-1,4-dicarboxylic acid diester **13** into cuneane-1,4-dicarboxylic acid diester **14** by chiral Pd-pincer catalyst **15**.

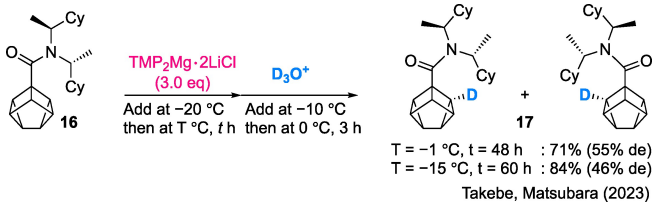


Entry	*t* / h	R in **13**	**14** / %	% ee
1	72	-CH_2CH_2Ph	31	67
2	72	-$CH_2CH_2pC_6H_4Br$	23	78
3	60	-$CH_2CH_2pC_6H_4F$	28	62

Takebe. Matsubara (2023)

This is the only example of asymmetric induction in the isomerization of cubane to cuneane, demonstrating "cubane skeletal editing" that can introduce an asymmetric environment in a single step while retaining the function of cubane as a bioisostere of benzene. This result also becomes very significant when considering that the structural isomerization following 2,6-cuneane in the scaffold editing, as shown in Scheme 5.

Among the chiral cuneanes shown in Figure 2, the 1,2-disubstituted derivatives can be obtained via DoM (Directed ortho Metalation). The major difference from cubane is that it does not require three substituents for having chirality in the cuneane case. Recently, we reported regioselective synthesis of 1,2-disubstituted cuneanes using *ortho*-metalation starting from 1-substituted cuneanes. All products of this technique (1,2-disubstituted cuneanes), as already mentioned, are chiral molecules. The asymmetric synthesis of 1,2-disubstituted cubanes using a chiral amide as a chiral auxiliary was also examined. Bis((*R*)-1-cyclohexylethyl)amine had been introduced in 1-cuneanecarboxamide **16**, which was selectively prepared by Ag+ catalyzed isomerization of the corresponding cubane. As reasonable diastereoselectivities were observed in the deprotonation of **16** (Scheme 7), the possibility for asymmetric induction using a chiral auxiliary was also implied.[19]



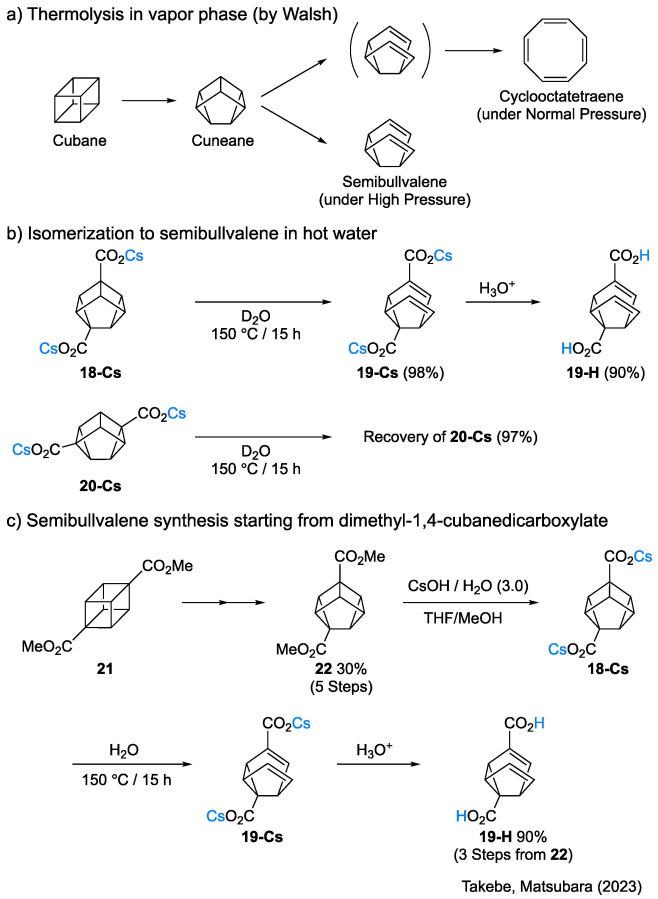
Scheme 7. Application of chiral auxiliary controlled DoM method to 1-cuneanecarboxyamide **16**.

3.2. Semibullvalene

Semibullvalene was first reported by Zimmerman and Grunewald in 1966.[20] Since then, it has attracted a lot of theoretical and experimental interest, particularly for its rapid Cope rearrangement leading to skeletal reorganization and its homoaromatic delocalized structure.[21] Its synthesis is based on a multi-step classical organic transformation reaction, and many semibullvalene derivatives have been reported. Recently, Xi et al. achieved the synthesis of polysubstituted semibullvalenes by metal-mediated C–C bond formation reactions.[22]

In addition to these conventional syntheses by build-up, semibullvalene synthesis by skeletal editing was recently reported by Takebe and Matsubara.[23] In the pyrolysis reaction of cubane in the gas phase, cuneane is isomerized via semibullvalene to cyclooctatetraene completely under ambient pressure, but as pressure increases, semibullvalene becomes dominant (scheme 8a).[17a] Hydrothermal conditions offer a feasible approach to achieve these high-pressure reaction environments.[24] Indeed, when dicesium cuneane-1,3-dicarboxylate was exposed to hot water at 150 °C for 15 hours, semibullvalene was quantitatively detected by ^{1}H NMR analysis. However, when dicesium cuneane-2,6-dicarboxylate was used as starting material, no semibullvalene was obtained, with complete recovery of the starting material (scheme 8b). The selective preparation of semibullvalene from dimethylcubane-1,4-dicarboxylate via dimethyl 1,3-cuneane carboxylate was demonstrated as shown in Scheme 8c.

It is important to note here that the structural isomerization following the scaffold-edited 1,3-disubstituted cuneane is stereospecific. Unfortunately, although 1,3-cuneans have received particular attention recently, there are so far no reports of asymmetric induction in the formation of the 1,3-isomer from 1,4-cubanes. This asymmetric expression would be a very important reaction, as would our asymmetric induction of 2,6-disubstituted cuneane.



Scheme 8. Scaffold editing from cubane to semibullvalene.

3.3. Cage Expansion

Polyhedral hydrocarbons that can be obtained by inserting a methylene group into the edges of cubane are classified as homocubane, bishomocubane, or trishomocubane,[25] depending on the number of inserted methylene groups. While homocubane with one inserted methylene group is achiral, bishomocubane obtained by introducing two methylene groups into the cubane skeleton has the potential to exhibit chirality (Figure 3a). There are four types of bishomocubane, of which only 1,3-bishomocubane is a chiral compound with C_2 symmetry (C_2-bishomocubane) (Figure 3b). When the molecule is twisted counterclockwise around the 1,4-axis of cubane by inserting methylene into the 2–3 and 5–6 edges, *M*-bishomocubane is formed. Thus, the chirality of C_2-bishomocubane can be explained through atropisomerism (Figure 3c). This expansion will be possible in the case of cuneane. The obtained 2,6-

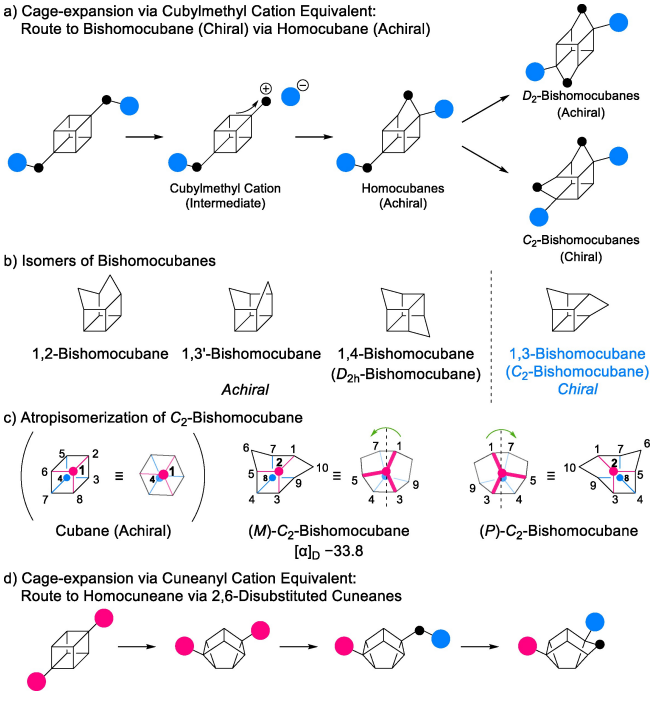


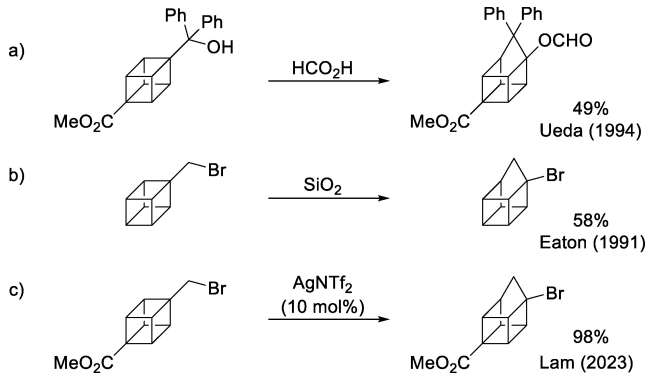
Figure 3. Cage expansion: a) Cubanes to bisohomocubanes via homocubanes; b) Isomers of bishomocubanes; c) Atropisomers of C_2-bishomocubane; d) Cunbanes to homocuneanes via cuneanes.

cuneane, which can be prepared as enantiomer rich form by our reaction can be transferred into a chiral homocuneane as shown in Figure 3d.

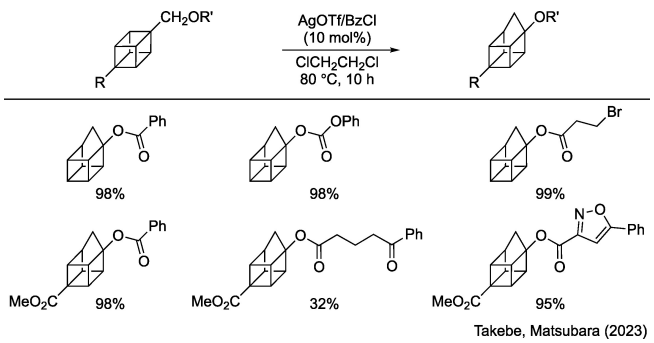
3.3.1. Homocubanes

Generating a cation on a carbon adjacent to the cubane is expected to drive cage expansion due to the strain release in the cubane. Wagner-Meerwein type rearrangements involving the formation of stable tertiary cations have already been reported (Scheme 9a).[12a] However, for broader use of cage molecules, unnecessary substituents are undesirable, and reactions involving difficult-to-generate primary cation equivalents are preferable. One example is the ring expansion reaction of bromomethyl cubane with SiO_2, as demonstrated by Eaton in 1991 (Scheme 9b).[26] Recently, the same reaction has been shown to proceed with silver catalysis (Scheme 9c).[18b] More desirable, however, is the rearrangement from acyloxymethyl cubane. This cage expansion results in a homocubane with an acyloxy substituent at the apex, enhancing its utility as a scaffold. The corresponding acyloxy substituted cubane is challenging to synthesize because its precursor, cubanol, is prone to ring opening.

Recently, we have discovered that the rearrangement to homocubane proceeds extremely efficiently when a catalytic amount of benzoyl triflate (available from silver triflate and benzoyl chloride *in situ)* was applied to acyloxymethyl cubane, which can be easily derived from cubane carboxylic acid ester.[27] The reaction showed good functional group tolerance, and it can be stated that a highly effective catalyst for this ring-expansion type of scaffold editing has been found (Scheme 10). However, it must be noted that the homocubanes generated from achiral 1,4-disubstituted cubanes are still achiral molecules.



Scheme 9. Ring expansion from cubanes into homocubanes.



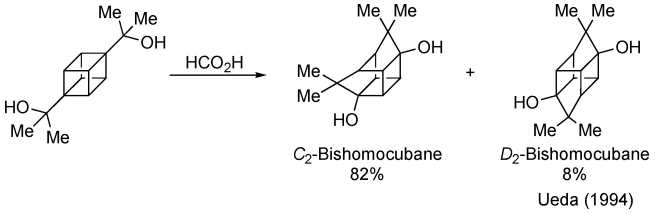
Scheme 10. Benzoyl triflate catalyzed isomerization of cubanes into homocubanes.

3.3.2. Bishomocubane

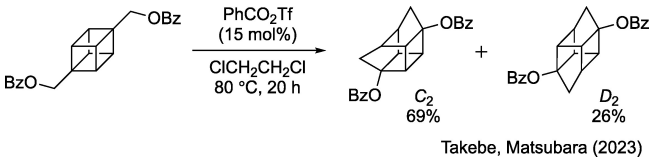
To create chiral scaffolds through ring expansion method, it is necessary to perform another stage of ring expansion from an achiral homocubane to make it a chiral C_2-bishomocubane. In the example provided by Ueda,[12a] it has been demonstrated that chiral C_2-bishomocubane acts as the major product in the Wagner-Meerwein type sequential ring-expansion of 1,4-bis(propan-2-oxy)cubane (Scheme 11).

When our catalyst, benzoyl triflate, was applied to 1,4-bis(benzoyloxymethyl)cubane, the resulting bishomocubane became a mixture of C_2 (chiral) and D_2 (achiral), with a ratio of 3 : 1 (Scheme 12).

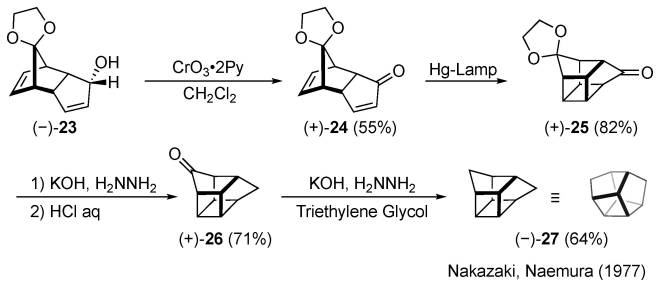
At the current stage, there are no successful examples of asymmetric induction in these cation-mediated rearrangements. Although it's not scaffold editing of cubanes, optically active C_2-bishomocubane has been synthesized in a buld-up manner. As shown in Scheme 13, synthesis of optically active 1,3-bishomocubane have been reported by Nakazaki.[28] Resolution of alcohol (−)-**23** was carried out by working with (+)-2-(1-aminoethyl)naphthalene as the resolving solvent agent. Collins' oxidation of the (−)-**23** gave (+)-**24**, which was dissolved in ether and irradiated with a medium-pressure mercury lamp to produce an 82% yield of (+)-**25**. To remove the functional groups and obtain C_2-bishomocubane, the Wolff-Kishner reduction was performed twice to give (−)-**27**.



Scheme 11. Acid catalyzed Wagner-Meerwein rearrangement of 1,4-bis(propan-2-oxyl)cubane into C_2-bishomocubane (chiral) and D_2-bishomocubanes (achiral).



Scheme 12. Benzoyl triflate catalyzed rearrangement of 1,4-bis(benzoyloxymethyl)cubane into C_2-bishomocubane (chiral) and D_2-bishomocubanes (achiral).



Scheme 13. Stepwise synthesis of optically active C_2-bishomocubane (−)-**27**.

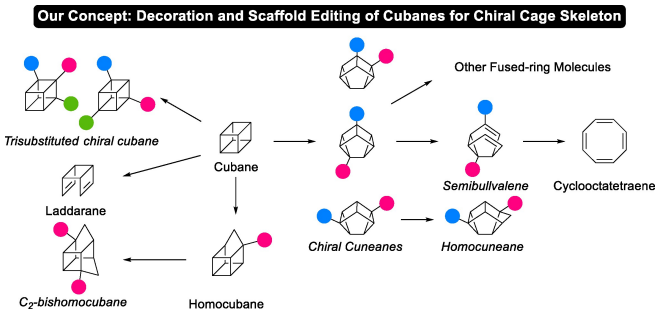


Figure 4. Prospects for the synthesis of chiral cage molecules using the decoration method and scaffold editing method starting from cubane.

C_2-bishomocubane has potential as a chiral scaffold. An efficient catalyst for cage expansion is beginning to be identified, but it is necessary to develop this catalyst system into an asymmetric catalyst. We are also considering this issue, but the development is expected to be challenging.

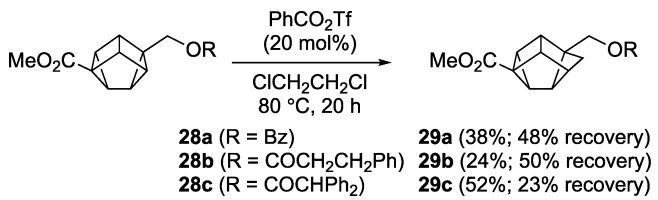
3.3.3. Homocuneane

As mentioned in the previous section, methods for inducing asymmetry in the synthesis of bishomocubane remain undeveloped. The transposition from acyloxymethyl cubane to homocubane is useful in that it involves direct substitution of oxygen atoms into the cage-like skeleton. Since successful asymmetric induction has been achieved in the isomerization from 1,4-cubanedicarboxylic acid diester to 2,6-cuneanedicarboxylic acid diester, it was decided to attempt ring expansion with this cuneane derivative. As shown in Scheme 14, treatment of cuneane derivatives **28** were treated with a catalytic amount of benzoyl triflate gave the corresponding homocuneanes **29**.[27] This method can be considered superior for utilizing acyloxy-substituted cage hydrocarbons as optically active substances.

4. Conclusions and Future perspectives

This concept focuses on chirality expression by substituent introduction into cubane with high symmetry and chirality introduction by cubane skeleton isomerization into polyhedral hydrocarbons with lower symmetry such as cuneane and bishomocubane. Cubane has attracted early attention as a bioisostere of benzene, because small hydrocarbon cages are desirable to anchor key molecular units in three-dimensional space, and Eaton's cubane meets these requirements. Furthermore, it is possible to introduce chirality by regioselective introduction of substituents. However, its synthesis is a complex multi-step process and a difficult site-selectivity problem that has not yet been completely solved. In order to develop a more efficient method for the synthesis of cage-like molecular skeletons with chirality, the possibility of rapid introduction of chirality by structural isomerization of cubane, i.e., cubane scaffold editing, in addition to chiral expression by "decoration" of cubane, has been explored. Figure 4 shows the polyhedral molecules that can be accessed by scaffold editing, starting from cubane. Surprisingly, as early as 1970, Eaton had already shown that cubane could be "editted" into different cage shapes by the use of silver, palladium, and rhodium catalysts. He also reported that silver and palladium catalysts could result in cuneans, while rhodium catalysts could result in radelanes.[29] For cuneane, there were fewer examples of isomerization reactions compared to skeletal transformation reactions starting from cubane. However, recently, skeletal transformation reactions using cuneane as a starting material have begun to be reported, and it is expected that the scaffold editing of cuneane will further diversify in the future. Conversion of cubane to homocubane and bishomocubane should also been attracting attention, and scaffold editing with the addition of chirality to C_2-bishomocubane is expected to be realized.

Many cage-type compounds have been synthesized by cycloaddition or condensation reactions – build up manner. However, many of these reactions are very complicated and lack functional group tolerance, making it difficult to introduce them as substructures of bioactive molecules. For such compounds, cubane is very stable, highly symmetric, and can be introduced as a substructure. We believe that the method of introducing cubane and then adding chirality by scaffold editing to increase complexity will have significance in the future.



Scheme 14. Rearrangements of cuneanes **28a–c** into homocuneanes **29a–c**.

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Conflict of Interests

The authors declare no conflict of interest.

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[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] H. Takebe, S. Matsubara, *Synthesis* **2024**, *56*, 16–284.
[4] 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.
[5] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756; b) F. Lovering, *MedChemComm* **2013**, *4*, 515–519.
[6] a) N. Yoshino, Y. Kato, Y. Shimada, C. M. Williams, S. Matsubara, *Isr. J. Chem.* **2021**, *61*, 380–386; b) Y. Kato, C. M. Williams, M. Uchiyama, S. Matsubara, *Org. Lett.* **2019**, *21*, 473–475.
[7] 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.
[8] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016. **1991**, *38*, 303–306; b) R. Okude, G. Mori, A. Yagi, K. Itami, *Chem. Sci.* **2020**, *11*, 7672–7675; c) A. Fokin, P. R. Schreiner, R. Berger, G. H. Robinson, P. Wei, C. F. Campana, *J. Am. Chem. Soc.* **2006**, *128*, 5332–5333.
[9] Scaffold Hopping: a) G. Schneider, W. Neidhart, T. Giller, *Angew. Chem. Int. Ed.* **1999**, *38*, 2894–2896; b) Y. Hu, D. Stumpfe, J. Bajorath, *J. Med. Chem.* **2017**, *60*, 1238–1246.
[10] L. Cassar, P. E. Eaton, J. Halpern, *J. Am. Chem. Soc.* **1970**, *92*, 6366–6368.
[11] a) H. Takebe, S. Matsubara, *Eur. J. Org. Chem.* **2022**, DOI: 10.1002/ejoc.202200567; b) H. Takebe, S. Matsubara, *Chem. Lett.* **2022**, *51*, 754–755.
[12] a) T. Hasegawa, Y. Kimura, Y. Kuwatani, H. Higuchi, M. Hatanaka, I. Ueda, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 462–472; b) T. Hasegawa, Y. Kuwatani, H. Higuchi, I. Ueda, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3009–3014; c) E. W. Della, W. K. Janowski, *J. Org. Chem.* **1995**, *60*, 7756–7759; d) W. L. Dilling, *J. Org. Chem.* **1993**, *58*, 5338–5344.
[13] N. Grover, M. O. Senge, *Synthesis* **2020**, *52*, 3295–3325.
[14] a) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316; b) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560.
[15] E. A. Anderson, R. E. McNamee, A. L. Thompson, *J. Am. Chem. Soc.* **2021**, *143*, 21246–21251.
[16] H. Takebe, N. Yoshino, Y. Shimada, C. M. Williams, S. Matsubara, *Org. Lett.* **2023**, *25*, 27–30.
[17] a) K. Hasseurück, H.-D. Martin, R. Walsh, *Chem. Ber.* **1988**, *121*, 369–372; b) 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.
[18] a) J.-Y. Son, S. Aikonen, N. Morgan, A. S. Harmata, J. J. Sabatini, R. C. Sausa, E. F. C. Byrd, D. H. Ess, R. S. Paton, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2023**, *145*, 16355–16364; b) E. Smith, K. D. Jones, L. O'Brien, S. P. Argent, C. Salome, Q. Lefebvre, A. Valery, M. Böcü, G. N. Newton, H. W. Lam, *J. Am. Chem. Soc.* **2023**, *145*, 16365–16373; c) K. Fujiwara, S. Nagasawa, R. Maeyama, R. Segawa, N. Hirasawa, Y. Iwabuchi, *Chem. Eur. J.* **2023**, 10.1002/chem.202303548.
[19] H. Takebe, S. Matsubara, *Chem. Lett.* **2023**, *52*, 358–360.
[20] H. E. Zimmerman, G. L. Grunewald, *J. Am. Chem. Soc.* **1966**, *88*, 183–184.
[21] H. Jiao, R. Nagelkerke, H. A. Kurtz, R. V. Williams, W. T. Borden, P. von R. Schleyer, *J. Am. Chem. Soc.* **1997**, *119*, 5921–5129.
[22] C. Wang, J. Yuan, G. Li, Z. Wang, S. Zhang, Z. Xi, *J. Am. Chem. Soc.* **2006**, *128*, 4564–4565.
[23] H. Takebe, S. Matsubara, *Chem. Lett.* **2023**, DOI: 10.1093/chemle/upad010.
[24] D. Bröll, C. Kaul, A. Krämer, P. Krammer, T. Richter, M. Jung, H. Vogel, P. Zehner, *Angew. Chem. Int. Ed.* **1999**, *38*, 2998–3014.
[25] A. P. Marchand, *Chem. Rev.* **1989**, *89*, 1011–1033.
[26] P. E. Eaton, Y. C. Yip, *J. Am. Chem. Soc.* **1991**, *113*, 7692–7697.
[27] H. Takabe, S. Matsubara, *Chem. Eur. J.* **2023**, DOI: 10.1002/chem.202303063.
[28] M. Nakazaki, K. Naemura, *J. Org. Chem.* **1977**, *42*, 2985–2988.
[29] L. Cassar, P. E. Eaton, J. Halpern, *J. Am. Chem. Soc.* **1970**, *92*, 3515–3518.

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