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Scaffold Editing of Cubanes into Homocubanes, Homocuneanes via Cuneanes

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Dedication: To the esteemed Professor Eaton, who pioneered the realm of cubane-related chemistry

The selective synthesis of cage-type hydrocarbons through the editing of the highly symmetric molecule cubane can be anticipated as one of the efficient approaches. In this paper, we identify a catalyst that facilitates the efficient scaffold isomerization of cubanes into homocubanes. This approach, which involves the direct synthesis of homocubanol esters, is promising as a novel method for the synthesis of phenoxy bioisosteres. Additionally, we observed that the isomerization of 1,4-bis-(acyloxymethl)cubane results in the generation of both D_2- and C_2-symmetrical bishomocubanes. The same catalyst was also applied to the isomerization of acyloxymethylcuneanes, producing homocuneanol esters.

Professor Eaton's pioneering research has not only sparked interest in the synthetic chemistry of cubane, a unique hexahedral hydrocarbon, but also initiated discussions on the potential of molecules containing cubane.[1] This ignited significant interest in its pharmaceutical applications, particularly as a benzene bioisostere.[2] The strategy of substituting a benzene ring with cubane to potentially enhance the activity of bioactive compounds has been explored extensively. Of the three isomers of disubstituted benzene (*ortho*, *meta*, and *para*), cubane research has largely centered on the *para*-position, aligning with 1,4-disubstituted cubanes. This focus is due to the prevalent use of *p*-disubstituted benzene derivatives in pharmaceuticals[3] and the synthetic feasibility of 1,4-disubstituted cubanes.[4] While cubane provides improved metabolic stability over benzene,[2a] its potential as a phenoxy bioisostere is especially compelling. However, the precursor molecule, cubanol, tends to undergo ring-opening reactions more readily than cubane itself via oxygen-based anionic or cationic pathways.[5] This complicates the integration of cubanol into bioactive molecules. As an alternative to using cubanol, a proposed method involves employing a Wagner–Meerwein-type rearrangement to convert readily synthesized cubylmethanol esters into acyloxyhomocubanes (Figure 1a).[6] Beyond the chemistry of the Platonic solid "cubane", Professor Eaton revealed the potential for isomerizing cubanes into various polyhedral structures. In 1970, he introduced a silver(I) or palladium(II)-catalyzed transformation of cubanes into cuneanes, which are stable three-dimensional frameworks that also have potential as benzene bioisosteres.[7] More recently, we published findings on a catalytic asymmetric synthesis of 2,6-disubstituted cuneanes, derived from the structural isomerization of 1,4-disubstituted cubanes.[8] This underscored the versatility of cubane skeletal isomerization in devising new chiral scaffolds and bioisosteres. During our research for scaffold editing of cubanes using Ag-based catalyst, we found a novel catalyst that efficiently isomerizes acyloxymethylcubanes into 1-acyloxyhomocubanes efficiently. In this isomerization, the sequential isomerization of 1,4-bis(acyloxymethyl)cubanes gave the corresponding bishomocubanes stereoisomeric mixtures. This mixture consists of both D_2-symmetric and C_2-symmetric entities, and it should be noted that the latter is a chiral

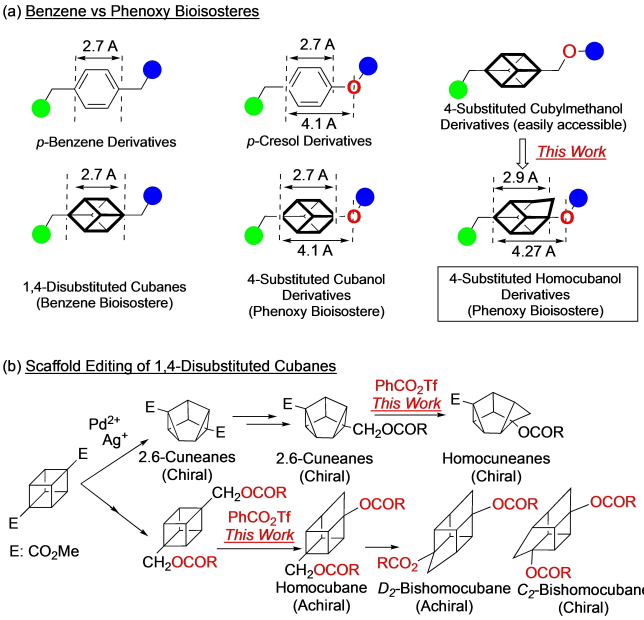

Figure 1. (a) A use of homocubanes as phenoxy bioisostere. (b) Scaffold editing strategy of 1,4-disubstitutted cubanes into other hexahedrons by $PhCO_2Tf$ catalyst.

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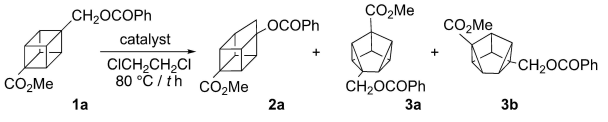
compound. Moreover, the same catalyst converted acyloxymethylcuneane to its ring-enlarged counterpart, homocuneanol ester.

The isomerization of cubane to cuneane upon reaction with Ag(I) salts was reported by Eaton in 1970, and has been the subject of more detailed investigations in recent years.[9] Indeed, when a catalytic amount of AgOTf is applied to methyl 4-benzoyloxymethyl-1-cubanecarboxylate **1a**, a 1,3-substituted cuneane is primarily produced (Table 1, entry 1). However, when a combination of an equimolar amount of benzoyl chloride and AgOTf is added to this reaction, there is no isomerization to cuneane at all, and it was found that homocubane **2a** can be quantitatively obtained (entry 2). Benzoic anhydride had no effect, and silver chloride itself has no catalytic activity (entries 3, 4). It was already known that a mixture of benzoyl chloride and AgOTf affords benzoyl triflate,[10] so **1a** was treated with 10 mol% of benzoyl triflate to afford **2a** in 93% yield (entry 5). The longer reaction period was necessary in the case of 5 mol% catalyst (entries 6, 7). It was also possible to obtain an active catalyst in combination with acetyl chloride (entry 8) instead of benzoyl chloride. To adjust the catalyst for the reactions to be shown later, a mixture of PhCOCl and Ag(I), which forms $PhCO_2Tf$ *in situ*, was used in the following examples in Scheme 1, instead of benzoyl triflate itself.

While the syntheses of homo- and bishomocubanes have been well studied from the viewpoint of the "build-up" method via cycloaddition and cyclization,[6a] there are limited reported cases of the Wagner-Meerwein type rearrangement from cubane to homocubane. For instance, there are acid-catalyzed reactions of cubane derivatives bearing a tertiary alcohol group on the cubane,[6b,c] and the rearrangement of bromomethylcubane to bromohomocubane in the presence of SiO_2[11] or $AgNTf_2$.[9b] To date, no efficient catalysts have been reported for the rearrangement of esters of cubylmethanol, a primary alcohol, except in the present case. As depicted in Scheme 1, various cubanes **1** were treated with the *in-situ*-prepared $PhCO_2Tf$ from 10 mol% of AgOTf and PhCOCl at 80 °C for 10 hours. In most cases, homocubanes **2** were obtained quantitatively. Not only esters but also carbonates yielded the corresponding homocubanes **2d** and **2f** quantitatively. To understand the scope of this method, the functional group tolerability was also examined (**2h**–**l**). As reported, benzoyl triflate acts as an efficient benzoylation reagent for alcohols;[12] hence, cubane precursors with a nucleophilic site might affect the catalytic activity. While the isomerization of substrates with a β-bromo ester (**2h**), γ-ketoester (**2i**), and oxazole (**2j**) proceeded in reasonable yields, those with a strong basic pyrazole (**2k**) and *N*-Boc protected amino acid ester (**2l**) resulted in the recovery of starting materials. As mentioned, the transformation from cubane to homocubane allows the direct substitution of the acyloxy group with a cage hydrocarbon. Considering that cubane serves as a benzne bioisostere, it suggests that homocubane, a molecule of a similar size, could be utilized as an equivalent to phenoxy bioisostere via this molecular editing protocol. Benzoyl triflate had been used as a stoichiometric reagent for a ring expansion of adamantyl aldehyde via activation of aldehyde group.[13] In the current homocubane formation reaction, it serves as a catalyst for the rearrangement via the activation of the acyloxy group (Scheme 2).

Although homocubane itself doesn't exhibit chirality, the sequential isomerization of 1,4-acyloxymethylcubanes might

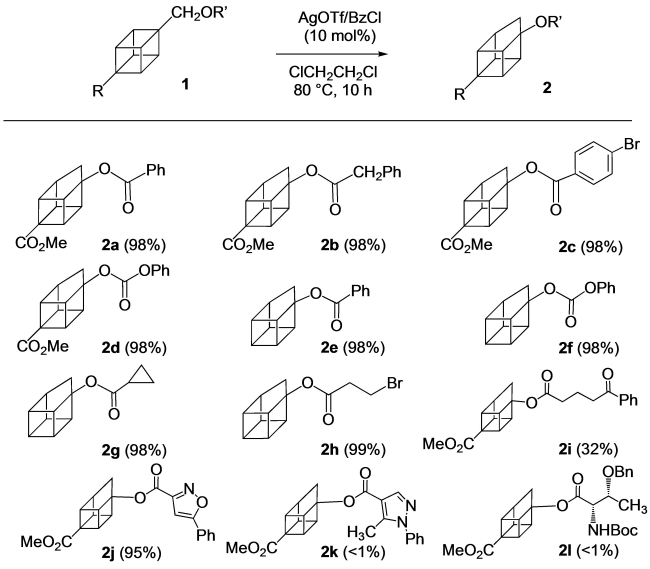
Table 1. Isomerization of cubane **1a**.[a]



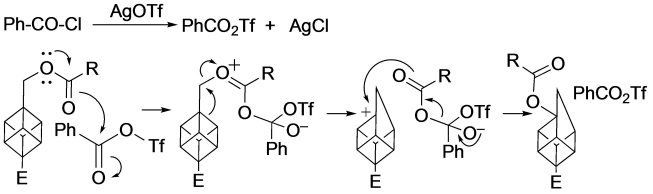
1a 2a 3a 3b

entry	Catalyst (mol%)	*t* h	2a	3a	3b	1a
1	AgOTf (10)	12	0	87	5	0
2	AgOTf (10) + PhCOCl (10)	12	98	0	0	0
3	AgOTf (10) + $(PhCO)_2O$ (10)	12	0	75	8	0
4	AgCl (30)	12	0	0	0	98
5	$PhCO_2Tf$ (10)	12	93	0	0	0
6	AgOTf (5) + PhCOCl (5)	12	65	0	0	30
7	AgOTf (5) + PhCOCl (5)	20	98	0	0	0
8	AgOTf (5) + AcCl (5)	20	90	0	0	0

[a] **1a** (0.2 mmol), AgOTf (0.1 M solution of CH_3CN/1,2-dichloroethane (5/95)), and additive (0.1 M solution of 1,2-dichloroethane) were used.



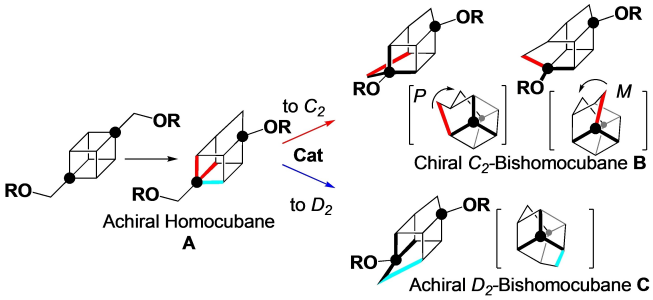
Scheme 1. Isomerization of acyloxymethylcubanes **1** into acyloxyhomocubanes **2**.



Scheme 2. Plausible explanation of isomerization to homocubane.

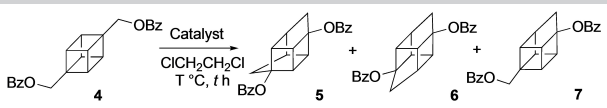
afford chiral bishomocubane. In the achiral homocubane **A**, three C–C bonds potentially undergo rearrangement (two red and one blue bonds in Scheme 3). If the blue-colored bond cleaves, achiral D_2-bishomocubane **C** forms. When either of the two red bonds breaks, it results in the chiral C_2-bishomocubane **B**, generating a pair of enantiomers. Various isomerization catalysts, in-situ prepared by different combinations of various silver salts and acyl chlorides, were examined that the product ratio between C_2- and D_2-forms would change. As shown in Table 2, the ratio remained almost unchanged in all cases. It is possible to examine the asymmetric synthesis using optically active acyl chlorides and optically active silver salts. Neither homocuneane nor bishomocubane formation was observed (see SI).

In the absence of a sufficient amount of catalyst or at low reaction temperatures (50 °C), the formation of homocubane **7** was observed (entries 1, 2). By increasing the catalyst amount to 15 mol%, the two types of bishomocubanes (**5** and **6**) were produced in approximately a 2:1 ratio. Whether using $PhCO_2Tf$ directly or the bulky carboxylic acid chloride MesCOCl as a catalyst precursor, the product ratio between C_2 (**5**) and D_2 (**6**) remained approximately 2:1. This aligns with the ratio of C–C bonds involved in the rearrangement (two red and one blue bonds in Scheme 3). When the counter-anion of the silver salt was changed to OMs or BF_4, the former showed no catalytic activity, while the latter experienced decreased activity (entries 6, 7). Hoping for reaction control imparted by chiral catalysts, Mosher's reagent, chiral phosphoric acid silver salts,[14] and (+)-CSA (camphor sulfonic acid) silver salt[15] were examined. However, none of these catalysts effectively promoted the rearrangement to homocubane. Additionally, a variety of other Lewis acids were investigated for their product ratios, but no positive outcomes were observed for the rearrangement. About the detail, see SI, Table S1.



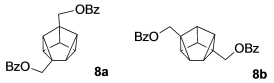
Scheme 3. Formation of C_2-(**B**) and D_2-homocubanes **C** via sequential rearrangements from 1,4-bis(acyloxymethyl)cubane using *in situ* prepared catalyst.

Table 2. Isomerization of Cubane 4.[a,b]



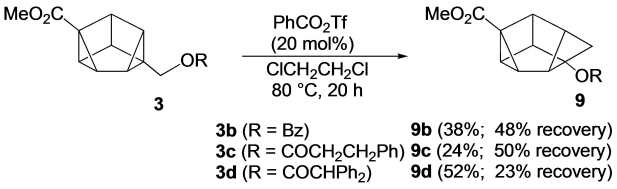
entry	Catalyst (mol %)	T °C/t h	5	6	7	4
1	AgOTf/PhCOCl (10)	80/10	42	17	35	< 5
2	AgOTf/PhCOCl (10)	50/10	48	18	29	< 5
3	AgOTf/PhCOCl (15)	80/10	68	27	< 5	< 5
4	$PhCO_2Tf$ (15)	80/10	69	26	< 5	< 5
5	AgOTf/MesCOCl (15)	80/12	69	27	< 5	< 5
6	AgOMs/PhCOCl (15)	80/10	0	0	0	> 95
7	$AgBF_4$/PhCOCl (15)	80/24	40	15	40	< 5

[a] **4** (0.2 mmol) was used. [b] Cuneane **8a** nor **8b** was not observed.



In scaffold editing from homocubane to bishomocubane, achieving asymmetric induction is crucial, especially in reactions accelerated by strain release. However, this process has proven to be exceptionally challenging. If one were to start with cuneane and undergo a rearrangement to produce "acyloxyhomocuneane", it would lead to the stereospecific conversion of chiral cuneanes. In simpler terms, after inducing asymmetry during cuneane synthesis, one would merely need to perform the rearrangement. Hence, we tested the catalytic effect of $PhCO_2Tf$ on the 2,6-disubstituted cuneane **3b** (Scheme 4). In fact, new cage compound **9b** was obtained in 38% yield. Other substrates, **3c** and **3d**, also yielded the corresponding **9c** and **9d**.[16] The yield cannot always be considered as favorable. The pentacyclo[4.3.0.$0^{2,4}$.$0^{3,9}$.$0^{5,8}$]nonane skeleton in compound **9** had been found during the photoisomerization of nortriquinacene by Paquette in the quest for his dodecahedron chemistry.[17]

As highlighted above, benzoyl triflate, primarily employed as a benzoylation reagent, has been definitively demonstrated to be exceptionally effective as a catalyst for the homologative ring expansion reactions of acyloxymethylcubanes. Although the catalyst proved effective for the ring expansion of acyloxymethylcuneanes into homocuneane, there's still a compelling need to develop a novel catalyst for this selective transformation. Conveniently, this catalyst can be synthesized *in situ* from AgOTf and benzoyl chloride. These acyloxy small cages, with an oxygen atom directly substituted onto them, show promise as phenoxy bioisosteres in a range of molecules. We've illustrated scaffold editing as a unique approach, distinct from complex cage hydrocarbon synthesis executed through various buildup methods.[17,18,19] The cornerstone of synthesizing optically active compounds lies in the asymmetric induction from cubane to cuneane, a technique we've already mastered. Therefore, scaffold editing starting from cubane holds considerable promise for the creation of new small molecular cages.



Scheme 4. Rearrangements of cuneanes **3b–d** into homocuneanes **9b–d**.

Supporting Information

The authors have cited additional references within the Supporting Information.[20,21,22] Deposition Numbers 2295366 (for **5**), and 2295821 (for **9 d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Scaffold Editing · Cubane · Homocubane · Bishomocubane · Homocuneane

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