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Stereoselective and Enantiospecific Synthesis of Trisubstituted 1,3a,4,6a-Tetrahydropentalene via Cuneane Scaffold Editing

Hiyori Takebe* and Seijiro Matsubara*

Cage-type hydrocarbons represented by cubane serve as molecular scaffolds for various useful molecules, such as pharmaceuticals and organocatalysts. However, even for the most readily available cubane, achieving regioselective substitution and controlled induction of chirality remains extremely challenging. A method to access chiral motifs using achiral 1,4-disubstituted cubanes, highly symmetric cage-type molecules, as starting materials has been developed. Through asymmetric isomerization of their molecular frameworks, these cubanes are converted into optically active 2,6-disubstituted cuneanes. Subsequently, treatment with nucleophiles, such as alcohols and 1,3-diketones, in the presence of a rhodium catalyst enables the stereoselective and enantiospecific synthesis of trisubstituted 1,3a,4,6a-tetrahydropentalenes via skeletal isomerization accompanied by nucleophilic addition. This cuneane scaffold editing strategy provides an efficient synthetic route to chiral 1,3a,4,6a-tetrahydropentalenes bearing substituents. These compounds show promise as asymmetric, cage-derived, bowl-shaped diene ligands.

1. Introduction

In 1964, Eaton developed an efficient method for synthesizing dimethyl 1,4-cubanedicarboxylate, a highly symmetric cubane derivative.[1,2] This perfectly cubic hydrocarbon exhibits remarkably high thermal stability, despite its inherent and substantial ring strain, an unusual property attributed to its high molecular symmetry. Walsh conducted thermodynamic calculations on the isomerization pathway from cubane to cyclooctatetraene (COT) via cuneane and semibullvalene, and demonstrated that this strain-releasing skeletal rearrangement is a highly exothermic process with an enthalpy change of 99 kcal mol^{-1} (**Scheme 1**a).[3] Notably, this isomerization represents a desymmetrization of the O_h-symmetric cubane core, whereby achiral monosubstituted or disubstituted cubanes can generate chirality through the initial transformation to C_2-symmetric cuneanes. This observation suggests the potential for developing new asymmetric synthetic strategies based on desymmetrizing skeletal rearrangement of the cubic scaffold. We recently introduced the concept of "cubane scaffold editing"[4] and demonstrated that chiral cuneane and semibullvalene derivatives bearing substituents can be stereoselectively synthesized from cubane through this strategy. Furthermore, this method also demonstrates that asymmetric induction via methylene insertion can be effectively achieved (Scheme 1b).[5–9]

In 1970, during investigations into the fundamental reactivity of cubane, Eaton and coworkers demonstrated that cubane can also isomerize to ladderane (tricyclo[4.2.0.0^{2,5}]octa-3,7-diene) upon treatment with [Rh(nbd)Cl]$_2$, indicating that this strain-releasing transformation can proceed even at low temperatures under transition metal catalysis (Scheme 1c, top).[10] This reaction has been thoroughly investigated by Williams and coworkers, who showed that the resulting ladderane further isomerizes to COT at 110 °C.[11] Thus, Williams demonstrated that in the rhodium-catalyzed conversion of cubane to COT, the reaction pathway does not involve cuneane as an intermediate, in contrast to the thermal process proposed by Walsh.

In fact, Eaton has reported that treating cuneane, generated and isolated from cubane using silver or palladium catalysts, with [Rh(nbd)Cl]$_2$ resulted in the formation of semibullvalene, which did not further convert to COT under these rhodium-catalyzed conditions. (Scheme 1c, bottom).[12] According to Walsh's study,[3b] the thermal isomerization of semibullvalene to COT proceeds at 270 °C, yielding an equilibrium mixture containing 2–4% semibullvalene and more than 95% COT. In fact, to date, no isolable compound corresponding to this pentalene intermediate has been reported. Thus, if the reaction proceeds solely via skeletal rearrangement of the cuneane framework, even under rhodium catalysis, the pathway through a pentalene intermediate

H. Takebe
Academic Center for Computing and Media Studies
Kyoto University
Yoshida-Honmachi, Sakyo, Kyoto 606–8501, Japan
E-mail: takebe.hiyori.5c@kyoto-u.ac.jp

H. Takebe, S. Matsubara
The Mitsui Chemicals & Kyoto University Digital Chemistry Laboratory
Kyotodaigalu-Katsura, Nishikyo, Kyoto 615–8510, Japan
E-mail: mataubara.seijiro.2e@kyoto-u.ac.jp

S. Matsubara
Institute for Liberal Arts and Sciences
Kyoto University
Yoshida-Honmachi, Sakyo, Kyoto 606–8501, Japan

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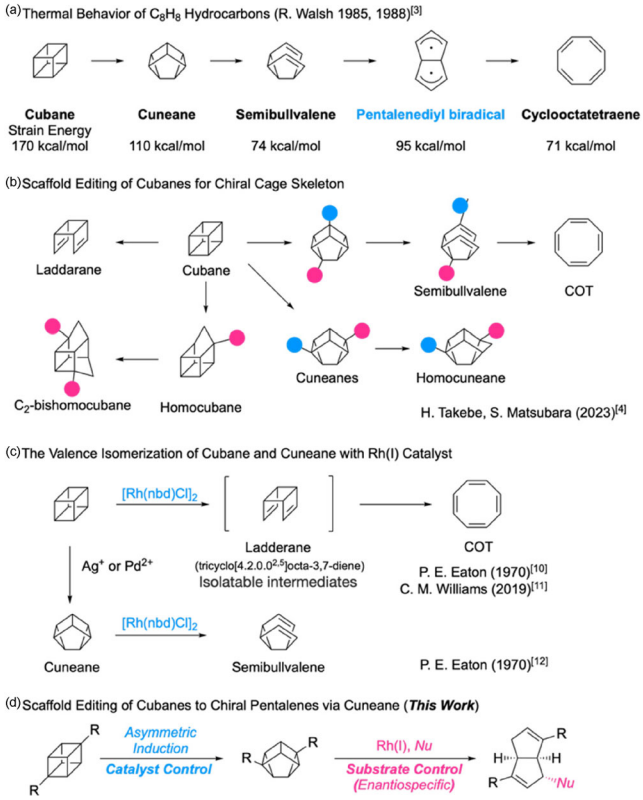

Scheme 1. a) Thermal isomerization of cubane to COT by Walsh. b) Concept of cubane scaffold editing to approach various cage-type compounds. c) Rh(I)-catalyzed valence isomerization of cubane and cuneane. d) Stereoselective and enantiospecific synthesis of trisubstituted 1,3a,4,6a-tetrahydropentalene via cuneane scaffold editing (This work).

tends to be unfavorable. On the other hand, the pentalene skeleton itself is less strained than semibullvalene; it should be formable and isolable. Therefore, we envisioned that, in addition to the isomerization of cuneane in Eaton's system, the introduction of an external nucleophile could incorporate a new reaction into the skeletal rearrangement. This would redirect the pathway toward one involving a nucleophilic addition, potentially enabling transformation into more stable products. Moreover, cuneane is a C_2-symmetric chiral compound, and when such chiral cuneanes are converted into pentalene frameworks, nucleophilic addition is expected to occur selectively from the exo face of the cage-shaped molecule due to steric hindrance. This spatial bias provides a strong basis for high facial selectivity. Most importantly, the chirality inherent in the cuneane framework should be retained throughout this transformation. In other words, the chirality introduced into cuneanes via asymmetric cubane scaffold editing can be preserved and further utilized to control the stereochemical outcome of subsequent addition reactions. We have previously succeeded in converting dimethyl 1,4-cubanedicarboxylate into optically active 2,6-disubstituted cuneanes through catalyst-controlled asymmetric rearrangement.[7c] We envisioned that subjecting this optically active, C_2-symmetric cuneane derivative to a skeletal rearrangement involving nucleophilic trapping would enable the construction of 1,3a,4,6a-tetrahydropentalenes bearing multiple stereogenic centers, while fully preserving the original chirality imparted by the cuneane scaffold (Scheme 1d). Based on these considerations, transition metal catalysis—particularly by low-valent rhodium complexes—was expected to be effective in promoting this transformation. We anticipated that in the process where Rh(I) interacts with the strained cuneane framework and the resulting semibullvalene skeleton to induce isomerization, the coexisting alcohol would also undergo oxidative addition, thereby generating a more active nucleophile. This would enable a nucleophilic reaction accompanying the skeletal isomerization, ultimately leading to the desired pentalene product. To explore this hypothesis, we investigated the Rh-catalyzed rearrangement of cuneanes in a presence of alcohol.

2. Results and Discussion

To evaluate working hypothesis, we subjected racemic dimethyl cuneane-2,6-dicarboxylate (**1a**) to a Rh(I)-catalyzed skeletal rearrangement in the presence of 2-phenylethanol as a nucleophile, using ethanol-free chloroform as the solvent (**Table 1**). Our initial focus was on screening various Rh(I) catalysts to identify optimal conditions. Among those tested, $[Rh(nbd)Cl]_2$ (entry 1) provided the best result, affording the desired tetrahydropentalene product racemic **2a** in 84% yield. This result established $[Rh(nbd)Cl]_2$ as the most effective catalyst for this transformation. In contrast, other Rh(I) complexes bearing different ligands (Entries 2–4, 6–10) afforded significantly lower yields. Notably, $[Rh(C_2H_4)_2Cl]_2$ and $[Rh(coe)_2Cl]_2$ led to negligible conversion, with only trace amounts of product detected. These findings suggest that the norbornadiene (nbd) ligand, which is π-accepting yet sufficiently labile, plays a crucial role in promoting the reaction. Given that the product features a diene-like moiety, the π-acidic and moderately dissociative character of nbd likely contributes to efficient catalyst turnover and stabilization of key intermediates. The cationic Rh(I) complex, $[Rh(nbd)_2]BF_4$ (Entry 5), afforded the product in a moderate yield of 23%, which was markedly inferior to its neutral counterpart. We next examined the role of the alcohol nucleophile. Under the optimized conditions using 2-phenylethanol (5.0 equiv), the reaction proceeded smoothly to give the tetrahydropentalene product in high yield (Entry 1). In sharp contrast, complete recovery of **1a** was observed in the absence of alcohol (Entry 12), indicating that the alcohol is essential for nucleophilic trapping of the skeletal rearrangement intermediate. Furthermore, in the absence of the Rh(I) catalyst (Entry 11), the reaction did not proceed at all, demonstrating that both Rh(I) catalysis and alcohol are indispensable components for this transformation. We also investigated the effect of alcohol loading. Increasing the amount to 10 equivalents (Entry 13) or decreasing it to 1.2 equivalents (Entry 14), both resulted in diminished yields, confirming that 5.0 equivalents of alcohol provide the optimal balance for efficient product formation. Finally, we investigated the influence of the solvent. Among the solvents tested, ethanol-free chloroform proved to be the most effective (Entry 1). In contrast, the use of other solvents, such as 1,2-dichloroethane

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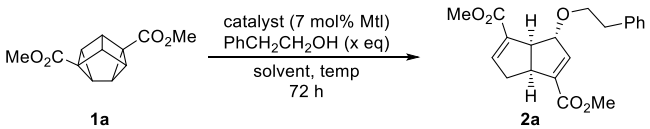
Table 1. Optimization of Rh-catalyzed isomerization of **1a** (Racemate) to **2a** (Racemate).



1a **2a**

Entry[a)]	Catalyst[b)]	x	Solvent	Temp [°C]	**2a**
1	$[Rh(nbd)Cl]_2$	5.0	$CHCl_3$	65	84
2	$[Rh(C_2H_4)_2Cl]_2$	5.0	$CHCl_3$	65	<1
3	$[Rh(cod)Cl]_2$	5.0	$CHCl_3$	65	2
4	$[Rh(coe)_2Cl]_2$	5.0	$CHCl_3$	65	<1
5	$[Rh(nbd)_2]BF_4$	5.0	$CHCl_3$	65	23
6	Rh(acac)(nbd)	5.0	$CHCl_3$	65	44
7	$Rh(acac)(C_2H_4)_2$	5.0	$CHCl_3$	65	<1
8	$[Rh(cod)OH]_2$	5.0	$CHCl_3$	65	28
9	$[Rh(cod)OMe]_2$	5.0	$CHCl_3$	65	31
10	$[Rh(nbd)OMe]_2$	5.0	$CHCl_3$	65	46
11	none	5.0	$CHCl_3$	65	<1
12	$[Rh(nbd)Cl]_2$	–	$CHCl_3$	65	<1
13	$[Rh(nbd)Cl]_2$	10	$CHCl_3$	65	51
14	$[Rh(nbd)Cl]_2$	1.2	$CHCl_3$	65	36
15	$[Rh(nbd)Cl]_2$	5.0	DCE[c)]	80	12
16	$[Rh(nbd)Cl]_2$	5.0	toluene	100	49
17	$[Rh(nbd)Cl]_2$	5.0	1,4-dioxane	100	34

[a)]**1a** (0.3 mmol) and solvent (3.5 mL) were used; [b)]nbd: norbornadiene, cod: 1,4-cyclooctadiene, coe: cyclooctene; [c)]DCE: 1,2-dichloroethane.

(Entry 15), toluene (Entry 16), and 1,4-dioxane (Entry 17), led to a significant decrease in yield.

With the optimized conditions in hand, we next explored the scope of nucleophiles using racemic **1a** as the substrate (**Scheme 2**). A range of primary linear alcohols reacted smoothly to afford the corresponding 1,3a,4,6a-tetrahydropentalene derivatives in good yields (**2a**–**2d**, **2g**, and **2m**). Secondary alcohol was also tolerated, furnishing the desired product in moderate yield (**2h**). Alcohols containing strained small-ring systems (**2e** and **2f**) and allylic alcohols (**2i** and **2j**) provided the products in low to moderate yields. Importantly, alcohols bearing functional groups—such as an ester moiety (**2k**) and a terminal alkyne protected with a trimethylsilyl (TMS) group (**2l**)—were compatible with the reaction conditions and afforded the corresponding tetrahydropentalenes. Remarkably, 1-naphthol (**2n**) and acetylacetone (**2o**) acted as carbon-based nucleophiles, delivering the desired products in good yields. These results underscore the versatility of this transformation and its broad tolerance toward functional groups and structural diversity.

To evaluate the enantiospecificity of this transformation, we performed a sequence of scaffold editing reactions starting from an achiral 1,4-disubstituted cubane derivative **3**, employing our previously reported method for the asymmetric isomerization of cubanes to cuneanes (**Scheme 3**). Following our established protocol,[7b,c] treatment of cubane **3** with a chiral Pd pincer complex and Ag(I) salt furnished enantiomerically enriched 2,6-disubstituted cuneanes, namely (*P*)-**1b** and (*M*)-**1b**. When these optically active cuneanes were subjected to the rearrangement conditions using $[Rh(nbd)Cl]_2$ and *n*-propanol, the corresponding trisubstituted pentalene product **4** was obtained with almost retention of stereochemical integrity. This result unambiguously demonstrates that the skeletal rearrangement from the optically active cuneane to the corresponding 1,3a,4,6a-tetrahydropentalene proceeds both in stereoselective and enantiospecific manner, preserving the chirality introduced at the cuneane stage. Thus, the pathway outlined in Scheme 3 represents a highly engineered synthetic module that enables the progression from achiral precursors to chiral intermediates and finally to other chiral products. Although the absolute configuration of the major enantiomer of compound **4** has not been determined experimentally, its likely stereochemical assignment is shown in Scheme 3. This assignment is based on the assumption that the inherent chirality of the caged compound cuneane is transferred stereospecifically to the product (see Figure S5, Supporting Information). This strategy highlights the strong potential of this methodology as a practical platform for the synthesis of chiral ligands and materials.

As previously mentioned, Eaton demonstrated that cuneane undergoes isomerization to semibullvalene in the presence of Rh(I); however, no further isomerization beyond semibullvalene was reported, suggesting that the reaction may have stalled at this

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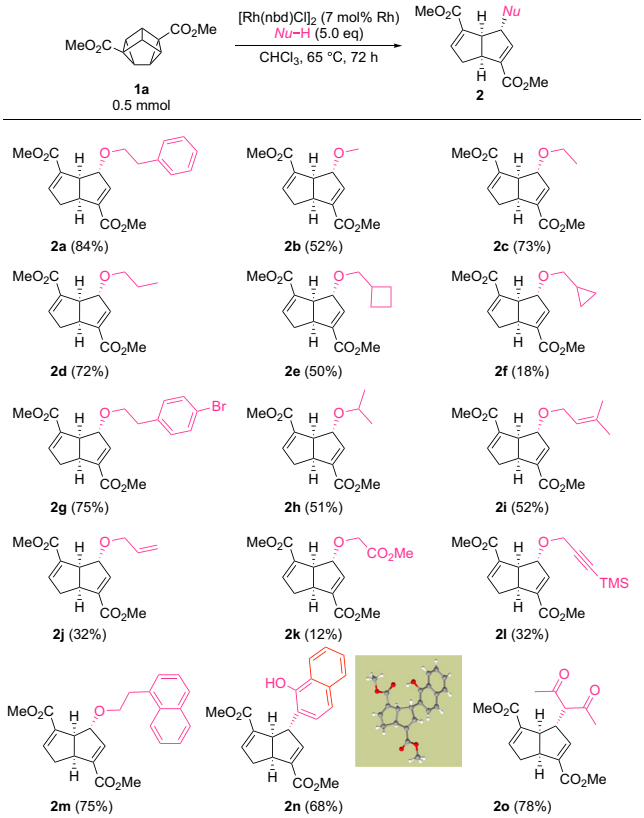
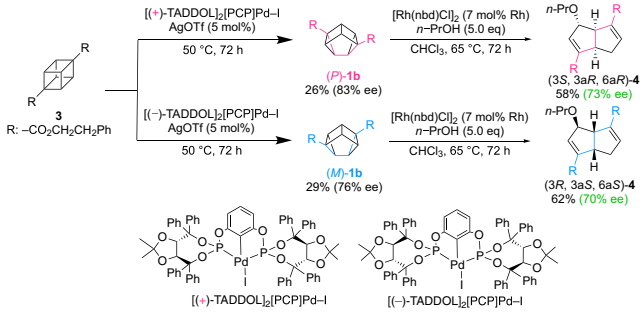


Scheme 2. Rhodium-catalyzed isomerization of racemic dimethyl 2,6-cuneanedicarboxylate (**1a**) in the presence of various nucleophiles to 1,3a,4,6a-tetrahydropentalenes **2** (racemates). See Supporting Information for X-ray crystal structure analysis of **2n** (Figure S4, Supporting Information, CCDC 2 441 028).



Scheme 3. Scaffold editing from cubane derivative **3** to optically active pentalene **4** via chiral cuneane **1b**. About absolute configuration of **4** was discussed in Supporting Information (Figure S5, Supporting Information).

stage. Although thermal isomerization from semibullvalene to the most stable COT via a pentalene intermediate requires heating to 270 °C, we have shown that simply introducing an alcohol as an external nucleophile allows the formation of a stable tetrahydropentalene derivative. Moreover, the successful use of 1,3-diketones (e.g., **2o**) as external nucleophiles, in addition to alcohols, and the reactivity of 1-naphthol (**2n**) as a carbon-based nucleophile suggests that the rhodium catalyst actively modulates the nucleophile's reactivity in this transformation. Furthermore, nucleophile addition appears to be stereoselective with respect to both the Nu and H components of the Nu–H moiety (as evidenced by reactions with MeOD; see Scheme S1 and Figure S1,S2,S3, Supporting Information), further implicating rhodium coordination in directing the facial selectivity of the nucleophilic trapping step (see Figure S5, Supporting Information). A detailed reaction mechanism is currently under investigation via Discrete Fourier Transformation (DFT) calculations, and the results will be reported in due course.

3. Conclusion

In this study, we have developed a synthetic method for trisubstituted 1,3a,4,6a-tetrahydropentalenes starting from 2,6-disubstituted cuneanes. This transformation not only represents the discovery of a new reaction, but also serves as a compelling demonstration of scaffold editing, wherein the core molecular framework is fundamentally restructured. The resulting tetrahydropentalene products exhibit a rigid, C_2-symmetric architecture, making them promising scaffolds for the design of chiral ligands and π-conjugated molecules.[13] Due to the coexistence of diene motifs and ester functionalities, these compounds may also serve as versatile platforms for asymmetric catalysis using Ir, Rh, or Pd complexes.[13–15] Moreover, this method demonstrates broad tolerance toward structurally and electronically diverse nucleophiles, underscoring its practicality and generality as a scaffold transformation strategy. The ability to convert this otherwise synthetically challenging framework in just two steps from a highly symmetric cubane precursor highlights its alignment with the principles of diversity-oriented synthesis[16] and molecular editing.[17] The transformation proceeds in a stereospecific and enantiospecific manner, and when enantioenriched cuneane substrates are employed, access to either enantiomer of the desired product is achieved. Taken together, these features establish this approach as a promising modular strategy for the synthesis of complex, functionally rich chiral molecules.

4. Experimental Section

Rel-Dimethyl (3*S*,3a*R*,6a*R*)-3-Phenethoxy-3,3a,6,6a-Tetrahydropentalene-1,4-Dicarboxylate (2a)

In a Schlenk tube, dimethyl cuneane-2,6-dicarboxylate (**1a**, 0.5 mmol, 110 mg) and norbornadiene rhodium(I) chloride dimer (0.017 mmol, 8.1 mg, 7 mol% Rh) were added. The internal atmosphere of the reaction vessel was replaced with argon by performing two cycles of evacuation and argon backfilling. Under Ar atmosphere, 3.5 mL of chloroform (EtOH free, passing through Al_2O_3 short column) was added and a pale yellow solution was obtained. To the solution, 2-phenylethanol (2.5 mmol, 305 mg) in 0.5 mL of chloroform was added. The mixture was stirred for 72 h at 65 °C (Using EYELA ChemStation PPM-5512A) under Ar atmosphere. After being cooled to room temperature, the mixture was passed through a silica gel short column. The obtained mixture was concentrated. Purification by a silica gel column chromatography (Yamazen Smart Flash EPCLC AI-580S; Hexane/AcOEt 4/1) gave the title compound **2a** in 82% yield (144 mg).[18–21]

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Supporting Information

The authors have cited additional references within the Supporting Information.[18–21]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: cubanes · cuneanes · pentalene · rhodium catalyst · scaffold editing

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