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Communication to the Editor

Substrate Specific Silver(I)-Catalyzed Cycloisomerization of Diene Involving Alkyl Rearrangements: Syntheses of 1,2,5,6-Tetrahydrocuminic Acid, *p*-Menth-3-en-7-ol, and *p*-Menth-3-en-7-al

Fuyuhiko Inagaki,* Mizuki Matsumoto,
Shisen Hira, and Chisato Mukai

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University; Kakuma-machi, Kanazawa 920–1192, Japan.

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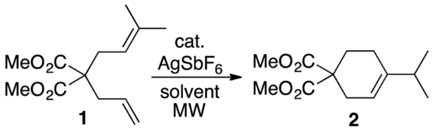
The novel cationic Ag(I)-catalyzed cycloisomerization, which is associated with alkyl rearrangements, from dimethyl 2-allyl-2-prenylmalonate (1) to dimethyl 4-isopropylcyclohex-3-ene-1,1-dicarboxylate (2) has been developed. Derivatization from the diester 2 into the diol 3 and its X-ray crystallographic analysis determined the structure. The mechanisms of the novel reaction were investigated by isotopic experiments, which supported the unusual alkyl shifts. In addition, the product 2 was used for the total syntheses of three natural products, 1,2,5,6-tetrahydrocuminic acid (12), *p*-menth-3-en-7-ol (13), and *p*-menth-3-en-7-al (14) in short steps.

Key words silver; catalytic reaction; cycloisomerization; diene; alkyl transfer

Coinage metal-catalyzed cyclizations of alkynes and other functionalities have been well developed.[1–5] In most cases, the alkynophilicities of metal elements, such as gold,[6–30] silver,[31,32] and copper,[33,34] have led to various types of reactions. In comparison with the catalytic reaction using a triple bond, the silver catalyzed reactions of simple alkene moieties are limited.[35–42] However, for example, the silver cation is often used in ion chromatography to separate a mixture of unsaturated fatty acids containing similar multiple double bond units.[43–50] Thus, we hypothesized that the coordination of the silver ion with two intramolecular alkenes might cause a novel cyclization under high temperature. We now report the novel silver-catalyzed cyclization of a diene, which is associated with alkyl rearrangement, and its application to natural product syntheses.

Initially, allyl prenyl malonate **1**[51–53] was used as the starting material. After several screenings using silver salts, we found that the condition with 20 mol% of $AgSbF_6$ in CH_2Cl_2 under microwave irradiation for 30 min afforded the dimethyl 4-isopropyl-3-cyclohexene-1,1-dicarboxylate (**2**) in 52% yield (Table 1, entry 1). Five mol% of $AgSbF_6$ also provided **2** in 59% yield (entry 2). Changing the solvent to 1,2-dichloroethane (DCE) gave **2** in 54% yield after 120 min at 120°C (entry 3), and increasing the temperature to 150°C led to the better yield (65%) and shorter reaction time (10 min) (entry 4). Other solvents like toluene, xylene, tetrahydrofuran (THF), and *ortho*-dichlorobenzene (ODCB) did not work for this reaction

Table 1. Ag(I)-Catalyzed Cycloisomerization of Diene **3**



Entry	$AgSbF_6$ (mol%)	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	20	DCM	100	30	52
2	5	DCM	100	120	59
3	5	DCE	120	120	54
4	5	DCE	150	10	65
5	5	Toluene	150	10	NR
6	5	Xylene	150	10	NR
7	5	THF	150	10	Trace
8	5	ODCB	170	10	NR
9	5	DCE	150	10	50[a]

a) 1 eq of BHT was added.

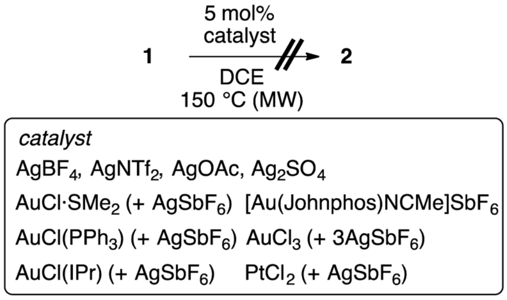


Chart 1. Treatment of Diene **1** with Several Catalysts

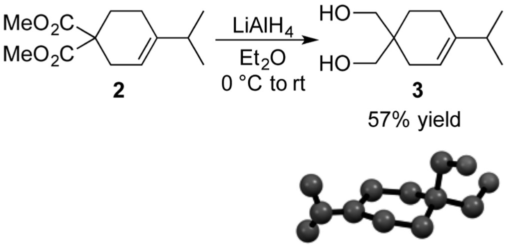


Chart 2. Derivatization for X-Ray Crystallographic Analysis

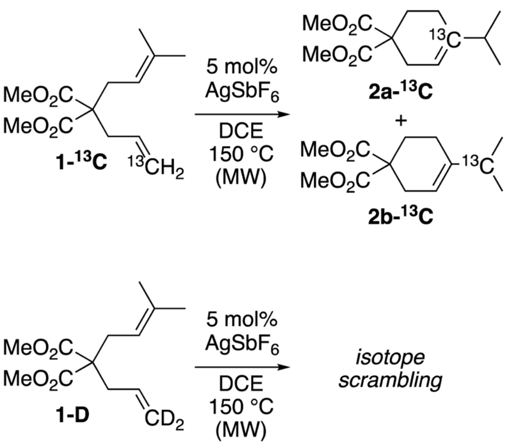


Chart 3. Isotope Labeling Experiments

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* To whom correspondence should be addressed. e-mail: finagaki@p.kanazawa-u.ac.jp

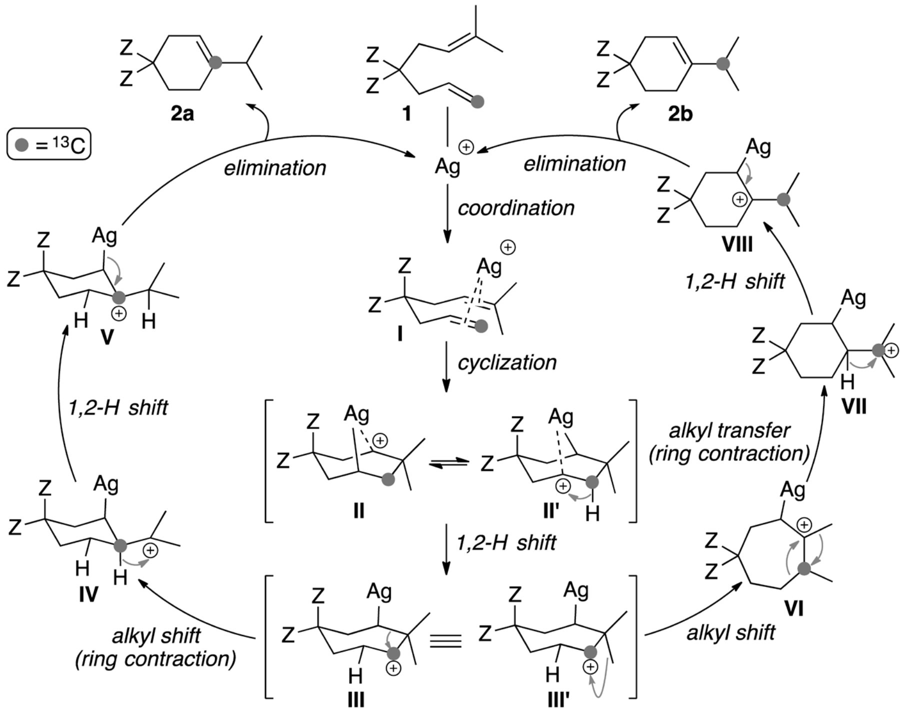

Chart 4. Plausible Mechanisms

(entries 5–8). Thus, the conditions of entry 4 seemed to provide the best reaction. Addition of butylated hydroxytoluene (BHT) as a radical scavenger in best condition also provided the desired **2** in 50% yield, which suggested that the reaction did not proceed *via* radical intermediates (entry 9). We next examined the different types of catalysts (Ag(I), Au(I), Au(III), Pt(II), *etc.*) for the same reaction (Chart 1). However, the desired **2** was not observed under all these conditions.

The structure of **2** was unambiguously elucidated by the reduction to form **3** and its X-ray crystallography (Chart 2). Next, we focused on the elucidation of the reaction mechanisms because production of the isopropyl moiety at the 4-position of product **2** induces an alkyl rearrangement. Thus, a carbon-13 (^{13}C) analysis using **1**-^{13}C was investigated. After the reaction under the best condition described for Table 1, entry 4, the resulting products showed two large ^{13}C-peaks at the C4 position (**2a**-^{13}C) and isopropylmethine carbon (**2b**-^{13}C) (Chart 3). A deuterated analysis using CD_2 instead of $^{13}CH_2$ (**1**-D) was also examined. However, the resulting product indicated deuterium scrambling. Based on these results, the plausible mechanisms are shown in Chart 4. At first, coordination of the silver cation with both double bonds of **1** would form **I**. Cyclization forming the 7-membered ring intermediates **II** and **II′**, and 1,2-H shift of **II′** might then provide the intermediate **III** (**III′**). In case of the alkyl shift *via* the ring contraction of **III** to construct the intermediate **IV**, the following 1,2-H shift and elimination of the silver cation would form product **2a**, which has a ^{13}C at the C4 position. On the contrary, methyl rearrangement for formation of the intermediate **VI** could follow the alkyl transfer accelerated by the ring contraction (**VII**). As the same process of **IV** to **2a**, **2b** having ^{13}C at the isopropylmethine position would be observed. The reason for the deuterium scrambling is uncertain. However, it might have occurred due to the uncontrollable 1,2-H shift of **II**, **II′**, **III**, and **III′**.

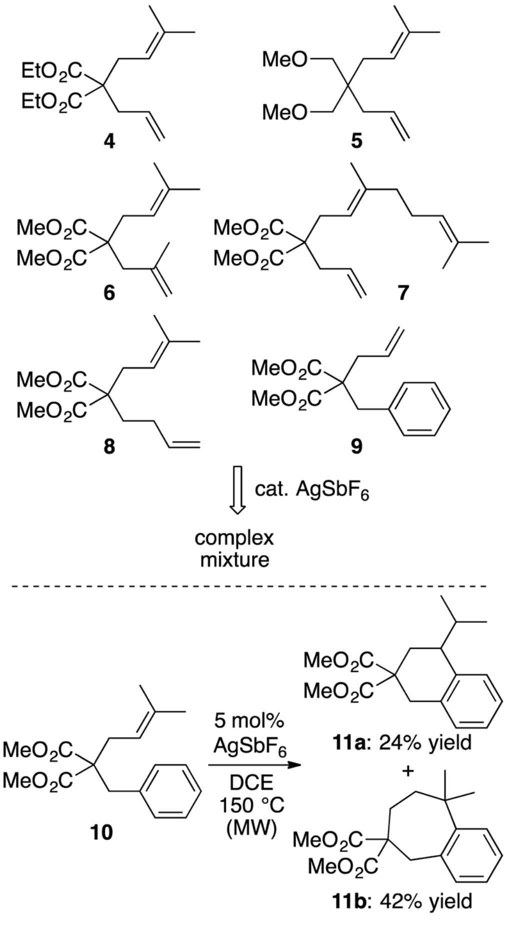

Chart 5. Trials for Silver(I)-Catalyzed Cyclization

Our next efforts focused on the scope and limitations of the similar cyclization associated with alkyl rearrangement. For this objective, allyl, homoallyl 3,3-dimethylallyl, 2-meth-

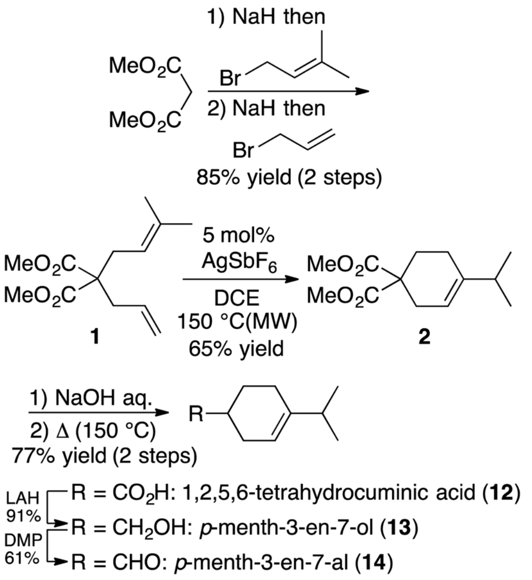

Chart 6. Syntheses of Three Natural Products

ylallyl, geranyl, and benzyl moieties were used for the diene functionalities of the starting materials **4**–**10** (Chart 5). Reactions of the dienes **4**–**9** caused undefined complex mixtures. When the benzyl prenyl unit **10** was reacted with the catalytic $AgSbF_6$, cyclized products **11a** and **b** were observed. A similar type of reaction has been reported using 10 mol% of the $Bi(OTf)_3 \cdot 4H_2O$ or $In(OTf)_3 \cdot H_2O$ catalyst.[54] Thus, we must conclude that the novel Ag(I)-catalyzed cyclization involving alkyl rearrangement only proceeded in diene **1**.

Our final task in this research is natural product syntheses. The, monoterpenoids, 1,2,5,6-tetrahydrocuminic acid (**12**),[55,56] *p*-menth-3-en-7-ol (**13**),[57] and *p*-menth-3-en-7-al (**14**),[58] which are isolated from the Cumin seed, Eucalyptus, and Yuzu, are now used as a fragrance (Chart 6). In addition, cumin oil has an antibacterial activity.[59] Nevertheless, methods for the syntheses of **12**–**14** are limited using classical strategies.[60,61] We accomplished the total syntheses of three natural products, 1,2,5,6-tetrahydrocuminic acid (**12**), *p*-menth-3-en-7-ol (**13**), and *p*-menth-3-en-7-al (**14**) *via* simple processes, *i.e.*, hydrolysis, decarboxylation, reduction, and oxidation from **2**, which was simply derived from dimethyl malonate in only 3 steps.

In summary, the novel cationic Ag(I)-catalyzed cycloisomerization *via* alkyl shifts of dimethyl 2-allyl-2-(3-methylbut-2-en-1-yl)malonate (**1**) formed dimethyl 4-isopropylcyclohex-3-ene-1,1-dicarboxylate (**2**). The structure of the resulting product **2** was unambiguously detected by an X-ray crystallographic analysis of **3**, which was derived from **2**. The mechanisms of the novel reactions were determined by isotopic experiments, which encouraged us to better understand the curious alkyl shifts. Although this type of reaction only proceeded from **1** in various dienes, the product **2** was useful for the syntheses of three natural products, *i.e.*, 1,2,5,6-tetrahydrocuminic acid (**12**), *p*-menth-3-en-7-ol (**13**), and *p*-menth-3-en-7-al (**14**) using a simple strategy. In addition, the product **4** from the novel reaction must have the potential for investigating the bioactivities by its derivatization. Thus, it was found that the cationic silver catalyst reacts with dienes at high temperature. Further development of the silver-catalytic reaction using a double bond is currently underway.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials (a: experimental procedures and characterizations, b: cif file for compound **3**).

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