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Effect of Added Salt on Ring-Closing Metathesis Catalyzed by a Water-Soluble Hoveyda–Grubbs Type Complex To Form N-Containing Heterocycles in Aqueous Media

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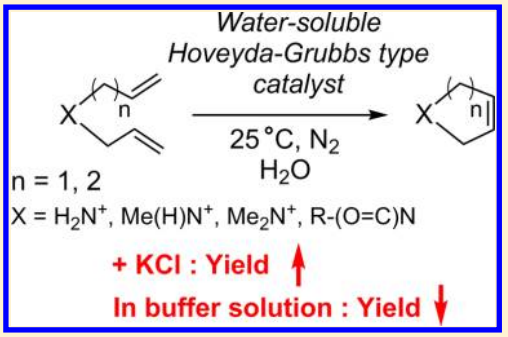
Supporting Information

ABSTRACT: The efficiency of ring-closing metathesis catalyzed by a Hoveyda–Grubbs type catalyst in water can be enhanced by addition of a chloride salt under neutral conditions. UV–vis spectroscopic study showed that a characteristic band of the catalyst around 380 nm remained over 16 h in the presence of KCl, whereas the band distinctly decreased in the absence of KCl. The disappearance of the band is ascribed to a displacement of a chloride ligand by a water molecule or a hydroxide anion. The spectral changes can be related to the metathesis activity. The experimental results indicate that avoidance of the chloride ligand loss is important to maintain the metathesis activity in water.



INTRODUCTION

Olefin metathesis catalyzed by ruthenium complexes, known as an effective method for constructing new carbon–carbon bonds,[1] is often conducted in nonpolar solvents such as dichloromethane. However, the recent development of ruthenium complexes with an N-heterocyclic carbene (NHC) ligand and a 2-alkoxybenzylidene ligand (so-called Hoveyda–Grubbs type catalyst) and its diverted catalysts[2] has prompted us to conduct olefin metathesis in protic organic solvents or water,[3] because these complexes are rather stable toward air and/or moisture. Olefin metathesis in water is useful for polar substrates and attractive from the viewpoint of development of eco-friendly chemical processes. In order to increase the solubility of the catalysts in protic media, ruthenium complexes with a polyethylene glycol moiety[4] or tertiary ammonium groups[2e,f,5] in ligands have been prepared. Furthermore, some of the Hoveyda–Grubbs type complexes have been applied as a biochemical research tool.[6] Preparation of artificial biocatalysts with olefin metathesis activity has also been attempted, where the ruthenium complexes were attached to proteins.[7]

However, the activity of metathesis-mediating ruthenium complexes in aqueous media is often decreased from that in organic solvents.[5c,8] Grubbs and co-workers successfully enhanced the catalytic activity for the ring-opening metathesis polymerization (ROMP) of norbornadiene derivatives in aqueous media under acidic conditions.[4b,5a] A similar strategy has also been employed for ring-closing metathesis (RCM) mediated by ruthenium complex conjugated proteins.[7a,b] However, other strategies to enhance the metathesis efficiency under milder conditions are desirable for acid-sensitive substrates and biomolecules.

One factor to decrease the catalytic activity of metathesis-mediating ruthenium complexes in aqueous media is the water-induced dissociation of a chloride ligand from the complex. The process is believed to be the principal deactivation pathway for these complexes in protic solvents.[9] It has been known that the chloride ligand significantly affects the metathesis reactivity of ruthenium complexes,[10] and some research examples have demonstrated that replacement of the chloride ligand with other anionic ligands can enhance or reduce the catalytic performance of the ruthenium complexes.[11,12] It has also been reported that the ligand exchange sometimes causes the formation of a dimerized complex, which can work as a precatalyst in organic solvents[13] or result in an inactive form.[14] Accordingly, the avoidance of chloride ligand loss will be another strategy to enhance the metathesis activity of ruthenium complexes in aqueous media.

In this paper, we demonstrate the effects of chloride salt on the catalytic activity of water-soluble ruthenium complex **1** (Chart 1).[5d] The ROMP activity of **1** increases in the presence of 1 equiv of hydrochloric acid.[5d] Furthermore, the loss of a chloride ligand in protic solvent has been suggested.[15] In this context, we propose that addition of chloride salt is useful for enhancing the catalytic activity of **1**-mediating RCM under neutral conditions in water. Concerning the application to biochemical experiments, the effect of buffer reagents that are often used for biochemical research on the catalytic activity was also investigated.

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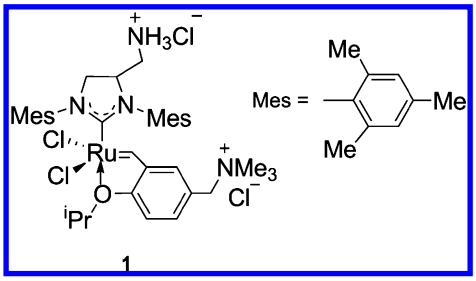
Chart 1. Structure of Water-Soluble Catalyst 1



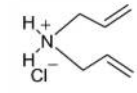
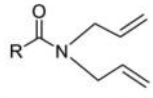
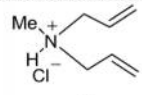
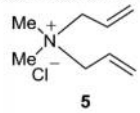
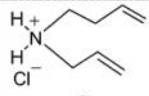
RESULTS AND DISCUSSION

Table 1 summarizes the effects of salt and buffer reagent on RCM to produce N-containing heterocycles in water. At first, we investigated the RCM of substrates **2** and **3**, the compounds employed in our previous work (entries 1−12).[7c] ^{1}H NMR spectra of the reaction mixtures for **2** and **3** are shown in Figures S1 and S2 (Supporting Information), respectively. Byproducts such as cycloisomerized compounds[4a,5d] were not detected. On the whole, compound **3** gave a higher product yield than **2**. This is due to the lack of electrostatic repulsion between **3** and catalyst **1**. The product yield was increased by potassium chloride (KCl) for both the substrates (entry 1 vs 2, entry 8 vs 9). In other words, the RCM activity in water can be enhanced under neutral conditions when a chloride salt is added to the reaction medium. Other inorganic salts such as KNO_3 were ineffective for enhancing RCM efficiency (entry 12).[16]

In contrast, the reactions in MES buffer (pD 6.4; MES = 2-morpholinoethanesulfonic acid) showed a decrease in product yield (entry 1 vs 3 and entry 8 vs 10). MES is one of the popular buffer reagents in biochemical reactions under weakly acidic conditions. A possible reason for the decrease in yield is that coordination of sulfonyl groups in a buffer molecule could occur, leading to the inhibition of the catalytic cycle. The addition of KCl brought out the slight recovery of the yield even in buffer solutions (entry 3 vs 4/5 and entry 10 vs 11), suggesting that the inhibition by the buffer reagent is caused by a reversible process (vide infra). However, the employment of HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), a buffer reagent for experiments under weakly basic conditions, brought about the inhibition of RCM even in the presence of KCl (entry 7). This is attributable to the increase in the concentration of hydroxide anion at the pH and may be associated with the ligand exchange between a chloride ligand and a hydroxide anion.

On the other hand, the tertiary ammonium species **4** gave no distinct RCM product in spite of KCl addition and showed a small amount of several unidentified peaks in the ^{1}H NMR spectrum (Figure S3 (Supporting Information) and entry 13 vs 14 (Table 1)). The quaternary ammonium species **5** did not produce a detectable amount of the RCM product (Figure S4 (Supporting Information) and entry 15 vs 16 (Table 1)). Compound **5** is basically poor in reactivity toward RCM catalyzed by various water-soluble ruthenium catalysts.[2f,4a,5d] These findings indicate that the RCM efficiency is not improved by the addition of KCl for intrinsically unreactive substrates. The utility of chloride salt addition was confirmed for the unsymmetrical ammonium species **6**, giving a six-membered-ring compound in RCM (Figure S5 (Supporting Information) and entry 17 vs 18 (Table 1)).

Table 1. Ring-Closing Metathesis (RCM) To Form N-Containing Heterocycles in D_2O[a]

Entry	Substrate	Added salt and/or buffer reagent	RCM yield (%)[b]
1	 **2**	Not added	18
2		100 mM KCl	32
3		10 mM MES[c,d]	0.8
4		10 mM MES + 100 mM KCl[c,d]	3.0
5		1 mM MES + 100 mM KCl[c,d]	4.5
6		1 mM MES + 100 mM KCl[c,d]	16
7		10 mM HEPES + 100 mM KCl[c,e]	<0.1[f]
8	 R = 1-β-D-Glc-O-$(CH_2)_2$- **3**	Not added	50
9		100 mM KCl	80
10		10 mM MES[c,d]	9
11		10 mM MES + 100 mM KCl[c,d]	40
12		100 mM KNO_3	47
13	 **4**	Not added	N.D.[f]
14		100 mM KCl	N.D.[f]
15	 **5**	Not added	0[g]
16		100 mM KCl	0[g]
17	 **6**	Not added	48
18		100 mM KCl	62

[a]Conditions: [substrate] = 8.4 mM; [**1**] = 5 mol %; reaction time 24 h; at 25 °C under N_2 in a tube with a J. Young valve. [b]Determined by ^{1}H NMR. [c]The acidity was calculated by using the relationship pD = pH + 0.4. [d]pD 6.4. [e]pD 7.4. [f]Not determined due to the appearance of several unidentified peaks in ^{1}H NMR. [g]Reaction time 48 h.

Next, the time dependence of the RCM reactions were investigated using compounds **2** and **3** (Figure 1). In reactions of both **2** and **3**, the initial reaction velocities increased in the presence of KCl. This tendency agrees with an increase in the overall yield by KCl. Furthermore, the effect on the reaction rates is dependent on KCl and buffer concentrations (see traces b−f in Figure 1A). It has been reported that the replacement of chloride ligand with another coordinating ligand affects the velocity of metathesis in organic solvents.[11a,12] In aqueous reaction media, a huge excess of water molecules and/or strongly coordinating hydroxide anions can replace a chloride ligand. Consequently, the observed effects of KCl and the buffer reagent on the RCM reaction rates can be related to the

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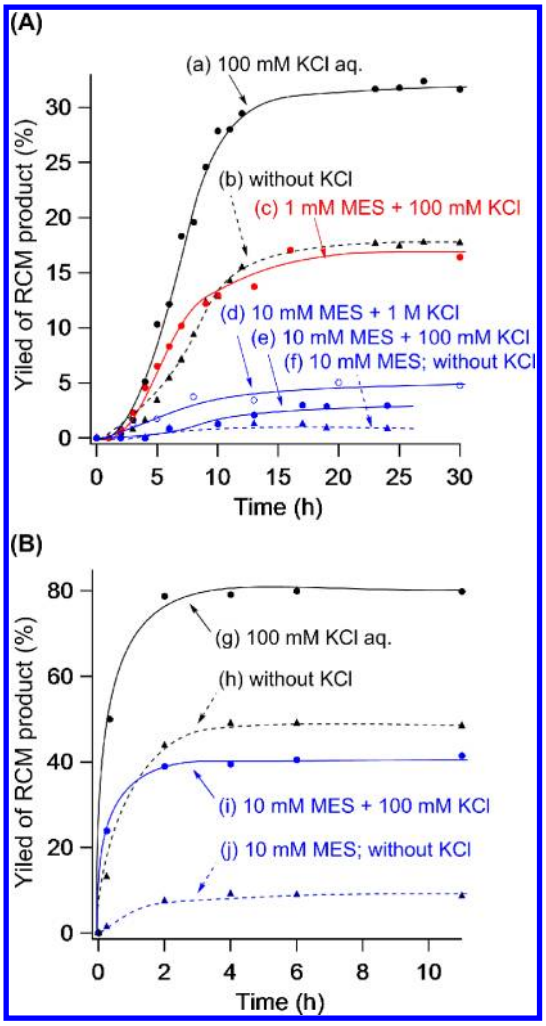

Figure 1. Time courses of RCM of **2** (A) and of **3** (B) catalyzed by **1** at 25 °C under N_2 ([substrate] = 8.2 mM, [catalyst 1] = 0.42 mM). Black, red, and blue indicate data taken in nonbuffered solutions, 1 mM MES (pH 6.0), and 10 mM MES (pH 6.0), respectively. Filled circles and triangles denote data obtained in the presence and absence of KCl, respectively.

ligand exchange of a chloride ligand with solvent molecules (vide infra).

The reactions of **2** reached the maximum yield around 15 h in all medium conditions employed, although no compound other than the starting material and the RCM product was detected in all reactions with **2**. This suggests that the catalysis deactivation occurred in parallel with the RCM reactions. One of the possible factors causing the catalysis deactivation is the ligand exchange at the metal center led by solvent molecules. However, other factors affecting the catalytic activity should also be taken into consideration, because the reaction of **3** is terminated at an earlier stage than that of **2** (around 4 h) in spite of the presence of KCl. On the basis of the fact that more rapid reactions are terminated at an earlier stage, the catalysis deactivation caused by the catalytic cycle also leads to the termination of the reaction as well as the catalysis deactivation in the absence of a substrate. One of the possible mechanisms of the substrate-inducing deactivation is inhibition by ethylene (5.41 ppm) produced as a coproduct. Another mechanism is the formation of a ruthenium hydride species via isomerization of a ruthenacycle intermediate.[17]

As described above, the lability of the chloride ligand in aqueous media is one of the probable factors affecting the RCM activity in water. In order to investigate this matter in detail, the stability of catalysis **1** in aqueous media was evaluated using UV−vis spectroscopy. Figure 2 shows typical UV−vis spectral

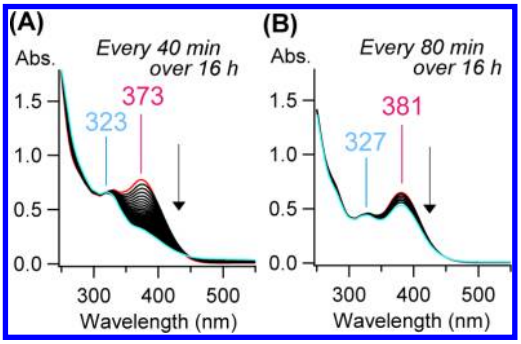

Figure 2. UV−vis spectral changes of **1** (89 μM) in aqueous solution at 25 °C under N_2: (A) in solution without KCl; (B) in aqueous KCl (100 mM). The solutions contain a small amount of MeOH (0.1% (v/v)). The spectra drawn as red and light blue lines in spectra A and B were taken at the start of measurements and after 16 h, respectively. The measurements were started on addition of a stock solution of **1** in MeOH to the aqueous solutions.

changes in the absence and the presence of KCl (100 mM). On dissolution of **1** in water without KCl, an MLCT absorption band appeared at 373 nm[18] and decreased over 16 h (Figure 2A). No RCM activity was observed even if substrate **2** or **3** was added further to the solution after 16 h. In other words, the chemical species finally formed was inactive with respect to RCM. In an aqueous solution of KCl (100 mM), the MLCT band appeared at 381 nm on addition of **1** to the aqueous solution, which is at a longer wavelength than that observed in the absence of KCl (Figure 2B). In contrast to the spectral change in the medium without KCl, the band at 381 nm remained even after 16 h. The band in a NaCl-containing solution appeared at the same wavelength as that in a KCl-containing solution (Figure S6, Supporting Information). These findings indicate that the added salt contributes to the stability in aqueous media, which is independent of a countercation. The wavelength of the band observed in the initial UV−vis spectrum is dependent on the concentration of KCl (381 nm in 100 mM KCl, 378 nm in 1 mM KCl (Figure S7, Supporting Information), and 373 nm in solutions without KCl). This indicates that rapid ligand exchange between a chloride ligand and a water molecule occurs during the mixing of a stock solution of **1** with an aqueous solution without KCl. In other words, the chemical species with the absorption band at 373 nm would be the state that a chloride ligand is partially lost from the metal center. The decrease in the absorption band around the wavelengths also depends on the concentration of KCl (Figure S8, Supporting Information). The effect of KCl on the spectral changes coincides with the catalytic activity of **1** (Table 1). After incubation of catalyst **1** in a non-KCl aqueous solution for 1 h, addition of KCl to the solution showed the shift of the absorption band from 373 to 381 nm (Figure S9, Supporting Information), which is similar to the spectrum initially observed in an aqueous KCl solution. Consequently, it can be concluded that a KCl-involving equilibrium step exists during the conversion into the catalytically inactive form over the period of the spectral change.

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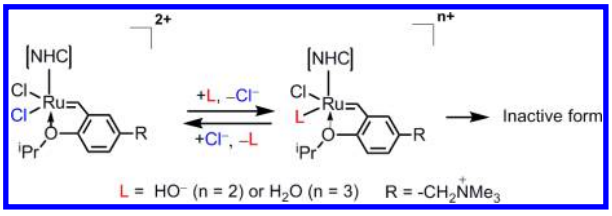
On the basis of the result of the UV−vis spectroscopic study, a plausible mechanism is depicted in Scheme 1. Additive

Scheme 1. Plausible Mechanism for the Effect of the Chloride Ligand[a]



[a]The numbers in right-corner of complexes indicate the overall charges of the complexes considering the charges on the metal center and on the ligands.

chloride salt contributes to the equilibrium shifting to the Cl-bound form, whereas a chloride ligand may be easily replaced by a water molecule or a hydroxide anion in the absence of a chloride ion source. This species may have reduced catalytic activity because of the more strongly coordinating character of water or hydroxide anion. A similar mechanism has been reported using a pyridine-substituted Ru complex in organic solvents.[11c] The intermediate will be gradually converted into the *completely* inactive form. The final form of the catalysts has not been identified at present. Although the ESI-TOF-MS spectrum (Figure S10, Supporting Information) obtained in the final stage suggested the formation of a Cl-bridged dimer, the structure is not clear at present because such chemical species in organic solvents can work as a precatalyst. Another possibility is an oxo-bridged form because of dissolution in water, although more experimental investigation is required to identify the catalytically inactive form in the future.

As indicated in Table 1, the RCM activity of **1** in buffer solutions dramatically decreased, even if KCl is present in the reaction media (e.g. entry 2 vs 4−7). Accordingly, the intrinsic stability of catalysis of **1** in buffer solutions was evaluated by the UV−vis spectral changes (Figures S11 and S12, Supporting Information). The absorption band of the initial spectrum in buffer solution appeared in the higher energy region, in comparison with that in nonbuffered solutions (λ_{max} 368 nm in 10 mM MES buffer and 360 nm in 10 mM HEPES buffer). The absorption bands distinctly decreased over 6 h. Recovery of the catalytic activity by addition of KCl was moderate in the buffer solutions. The experimental observations suggest that the decreased RCM yields in the buffer solutions are dominantly caused by the inhibition of the substrate binding process.

CONCLUSION

In order to conduct RCM mediated by a water-soluble Hoveyda−Grubbs type complex in water effectively, addition of chloride salt is both practical and useful. The method is applicable to secondary ammonium and amide substrates. Added chloride salt contributes to maintenance of the chloride-bound form of the Hoveyda−Grubbs catalyst in aqueous media. Furthermore, buffer solutions which are often used in biochemical experiments may cause a decrease in the metathesis activity, although the presence of chloride salt gives rise to recovery of yield. This knowledge will be useful for developing protocols of synthetic routes based on olefin metathesis in aqueous media and application of olefin metathesis in the field of biochemical research.

EXPERIMENTAL SECTION

General Comments. All manipulations were carried out in an N_2-filled glovebox or using conventional Schlenk techniques unless noted. All solvents were degassed by freeze−pump−thaw methods before RCM reactions. The ^{1}H NMR spectra were recorded on a JEOL ECP 400 MHz NMR spectrophotometer. The chemical shifts were referenced to TMS (in $CDCl_3$) or sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) (in D_2O). The UV−vis spectra were measured using a Shimadzu UV-2550 spectrophotometer with a thermostated cell holder. ESI-MS analysis was carried out using a JEOL JMS-T100LC mass spectrometer.

Catalyst **1**[5d] was synthesized in the same manner as given in a previous report, and the NMR data agreed with the reported data.[5d,7c] Compound **5** was purchased from Tokyo Chemical Industry Co., Ltd. (TCI) as a 60% aqueous solution and used as received. In the ^{1}H NMR measurements for the reaction of **5**, a presaturation technique for the peak derived from H_2O was employed to increase the spectral resolution and sensitivity. An authentic sample of the RCM product from **6** (**6-RCM**) was purchased from Wako Pure Chemical Industries Ltd. (Wako). The spectroscopic data of these compounds are indicated below. Other substrates and authentic products were obtained by neutralization of commercially available amines or by syntheses as described below. A buffer solution dissolved in D_2O was prepared from the corresponding H_2O solution. After the H_2O solution was concentrated by using an evaporator, the same volume of D_2O was added to the residue. This procedure was repeated three times.

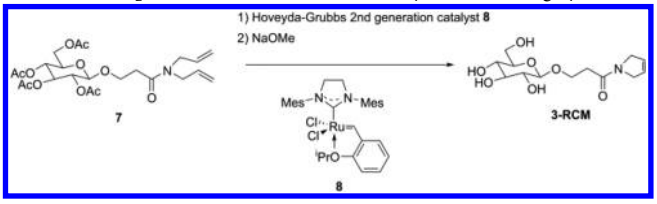
Evaluation of RCM Activity. A reaction mixture was prepared in a glovebox and charged into an NMR tube with a J. Young stopcock at 25 °C, and the RCM reaction was followed by ^{1}H NMR spectroscopy. The product yields were calculated on the basis of the peak intensities originating from the starting materials and products.

Compound 2.[3b] The corresponding free amine purchased from TCI was neutralized by HCl in ether. The precipitated white solid was quickly collected by suction and dried in vacuo. This compound is highly hygroscopic. ^{1}H NMR (D_2O, 400 MHz): δ 5.96−5.86 (m, 2H, $-CH{=}CH_2 \times 2$), 5.53−5.47 (m, 4H, $-CH{=}CH_2 \times 2$), 3.66 (d, J = 6.8 Hz, 4H, $-NCH_2CH{=}CH_2 \times 2$). ^{13}C NMR (D_2O, 100 MHz): δ 130.6, 126.3, 51.4.

Authentic Sample of RCM Product from 2 (2-RCM).[3b] 3-Pyrroline (free amine form of **2-RCM**) purchased from Wako was neutralized by HCl in ether. After the solvent was evaporated, the oily residue was dried in vacuo. ^{1}H NMR (D_2O, 400 MHz): δ 5.92 (s, 2H, olefinic protons), 4.08 (s, 4H, methylene protons). ^{13}C NMR (D_2O, 100 MHz): δ 127.4, 54.7.

Compound 3. The compound was synthesized according to the method reported in a previous report.[7c] ^{1}H NMR (D_2O, 400 MHz): δ 5.92−5.74 (m, 2H, $-CH{=}CH_2 \times 2$), 5.26−4.81 (m, 4H, $-CH{=}CH_2 \times 2$), 4.45 (d, J = 8.0 Hz, 1H, sugar-1′ H), 4.15 (m, 1H, $-OCH_\alpha CH_2(O{=}C)N-$), 4.05 (br, 2H, $-(O{=}C)NCH_2CH{=}CH_2$), 3.97 (br, 2H, $-(O{=}C)NCH_2CH{=}CH_2$), 3.90 (m, 2H, $OCH_\beta CH_2(O{=}C)N-$ and sugar-6′H_α), 3.70 (dd, J = 5.8, 9.6 Hz, 1H, sugar-6′H_β), 3.47 (dd, 1H, J = 9.3 Hz, 9.3 Hz, 1H, sugar-3′H), 3.43 (m, 1H, sugar-5′H), 3.36 (dd, J = 9.3 Hz, 9.6 Hz, 2H, sugar-4′H), 3.24 (dd, J = 8.0 Hz, 9.3 Hz, 1H, sugar-2′H), 2.79 (t, J = 6.2 Hz, 2H, $-OCH_2CH_2(O{=}C)N-$). ^{13}C NMR (D_2O, 100 MHz): δ 176.5, 135.1, 134.8, 119.1, 119.0, 105.3, 78.6, 78.4, 75.8, 72.3, 68.7, 63.4, 53.1, 51.3, 35.7.

Authentic Sample of RCM Product from 3 (3-RCM). The authentic sample of **3-RCM** was obtained by the following synthesis:



In a 50 mL two-neck flask equipped with a condenser, compound **7**[7c] (90 mg, 0.18 mmol) was dissolved in dry

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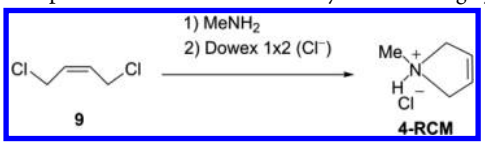
CH_2Cl_2 (5 mL) under a N_2 atmosphere. To the solution was added catalyst **8** (5.6 mg, 4 μmol, 5 mol %). The reaction mixture was stirred at 40 °C for 4.5 h. After the solvent was evaporated, the residue was subjected to silica gel column chromatography (elution: hexane/AcOEt = 4/1 → 1/1). The fractions with R_f = 0.45 on TLC (elution: hexane/AcOEt = 1/1) were collected, and the solvent was evaporated to yield a colorless oil. The material was dissolved in MeOH, and NaOMe (9.7 mg) was added. The solution was stirred at room temperature for 12 h. After addition of Dowex-50 WX8 cationic exchange resin (5.0 g), the solution was filtered. The solvent was evaporated to afford the compound **3-RCM** as a colorless oil (42 mg, 77% yield). ^{1}H NMR (D_2O, 400 MHz): δ 5.92−5.86 (m, 2H, olefinic protons), 4.65 (d, J = 8.2 Hz, 1H, sugar-1′H), 4.38 (br, 2H, −(O═C)NCH_2−), 4.19 (br, 3H, −(O═C)NCH_2− and −OCH_αCH$_2$(O═C)N−), 3.99 (m, 1H, −OCH_βCH$_2$(O═C)N−), 3.88 (dd, J = 2.1 Hz, 12.2 Hz, 1H, sugar-6′H_α), 3.71 (dd, J = 5.6, 12.2 Hz, 1H, sugar-6′H_β), 3.48−3.43 (m, 2H, sugar-3′ and 5′), 3.36 (dd, 1H, J = 8.2 Hz, 8.2 Hz, 2H, sugar-4′), 3.23 (dd, J = 8.0 Hz, 8.0 Hz, 1H, sugar-2′), 2.73 (t, J = 6.2 Hz, 2H, −OCH$_2$CH_2(O═C)N−). ^{13}C NMR (D_2O, 100 MHz): δ 176.5, 135.1, 134.8, 119.1, 119.0, 105.0, 78.6, 78.4, 75.8, 72.4, 63.5, 53.1, 51.9, 35.7. FAB-HR-MS (positive mode): calcd 304.1396 for $C_{13}H_{22}NO_7$ ([M + H]$^+$), found 304.1398.

Compound 4. The corresponding free amine purchased from Wako was neutralized by HCl in ether. After the solvent was evaporated, the oily residue was dried in vacuo. ^{1}H NMR (D_2O, 400 MHz): δ 5.92 (s, 2H, −CH═CH$_2$ × 2), 4.08 (s, 4H, −CH═CH_2 × 2), 3.83 (dd, 2H, J = 13.2 Hz, 7.6 Hz, −NCH_αCH═CH$_2$), 3.69 (dd, 2H, J = 13.2 Hz, 7.6 Hz, −NCH_βCH═CH$_2$), 2.81 (s, 3H, −NCH_3). ^{13}C NMR (D_2O, 100 MHz): δ 129.2, 128.4, 60.2, 41.4. Anal. Calcd for C_7H_{14}NCl: C, 56.94; H, 9.56; N, 9.49. Found: C, 56.70; H, 9.53; N, 9.29.

Authentic Sample of RCM Product from 4 (4-RCM).[19] The authentic sample of **4-RCM** was obtained by the following synthesis:

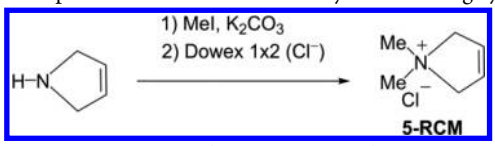


In a 100 mL two-neck flask with a dropping funnel, a 40% solution of methylamine in methanol (8 mL) was dissolved in THF (20 mL) and cooled with an ice bath. From the dropping funnel, *cis*-1,4,dichloro-2-betene (2.48 g, 20 mmol) in THF (10 mL) was slowly added to the methylamine solution. The solution was stirred at room temperature for 16 h. The reaction solution was poured into ice and acidified by concentrated HCl. The solution was washed with ether twice. The water phase was separated and was adjusted to pH ∼11 with 2 M aqueous NaOH. The solution was subjected to distillation. A fraction at 65−72 °C was collected to yield the free amine of **4-RCM** (1.10 g, 68% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (m, 2H, olefinic protons), 3.46 (m, 4H, methylene protons), 2.48 (s, 3H, methyl protons).

The free amine obtained above was dissolved in ether containing acetic acid and the solution evaporated. The residue was dissolved in MeOH. To the solution was added Dowex 1X2 (Cl$^-$) ion-exchange resin (3 g). The suspension was stirred for 10 min and filtered. After the solution was evaporated, the resultant residue was dissolved in a minimum amount of MeOH and ether was added to form a white solid. The white solid was quickly collected, rinsed with ether, and dried in vacuo to give **4-RCM** as a highly hygroscopic solid. Due to its hygroscopicity, the yield was not precisely evaluated. ^{1}H NMR (D_2O, 400 MHz): δ 5.92 (m, 2H, olefinic protons), 4.39 (d, J = 13 Hz, 2H, −NCH_αCH═CH$_2$), 3.92 (d, J = 13 Hz, 2H, −NCH_βCH═CH$_2$), 3.02 (s, 3H, methyl protons). ^{13}C NMR (D_2O, 100 MHz): δ 127.2, 64.5, 44.6. EI-MS (positive mode): m/z 84 ([M − Cl]$^+$), 69 ([M − Cl − CH$_3$]$^+$), 57 ([M − Cl − NCH$_3$]$^+$).

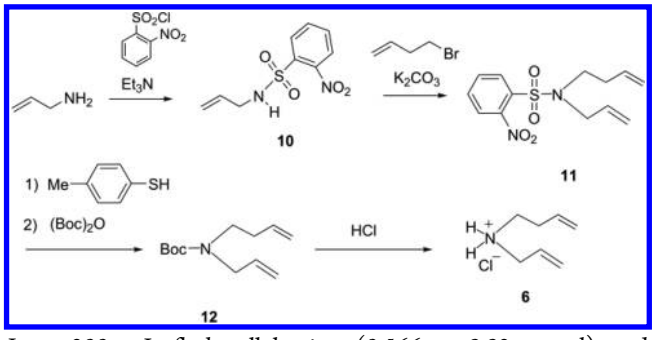
Spectroscopic Data of Compound 5. ^{1}H NMR (D_2O, 400 MHz): δ 6.04 (m, 2H, −CH═CH$_2$ × 2), 5.71(m, 4H, −CH═CH_2 × 2), 3.89 (d, 4H, J = 7.4 Hz, −NCH_2CH═CH$_2$−), 3.01 (s, 6H, -NCH_3 × 2). ^{13}C NMR (D_2O, 100 MHz): δ 131.8, 127.0, 68.8, 52.1. EI-HR-MS (positive mode): calcd 98.0964 for $C_6H_{12}N$ ([M − Cl]$^+$), found 98.0970.

Authentic Sample of RCM Product from 5 (5-RCM).[4] An authentic sample of **5-RCM** was obtained by the following synthesis:



In a 100 mL flask, K_2CO_3 (4.0 g, 29 mmol) was suspended in 20 mL of EtOH. To the suspension were added 3-pyrroline (0.201 g, 2.9 mmol) and MeI (0.803 g, 5.8 mmol). The solution was stirred at room temperature for 2 h, and the insoluble materials were removed by filtration. After the solvent was evaporated, the residue was dissolved in 60 mL of EtOH. To the solution was added Dowex 1X2 (Cl$^-$) ion-exchange resin (5 g). The suspension was stirred for 10 min and filtered. After the solvent was evaporated, the compound **5-RCM** was obtained as a white solid (0.281 g, 73%). ^{1}H NMR (D_2O, 400 MHz): δ 5.96 (m, 2H, olefinic protons), 4.33 (s, 4H, methylene protons), 3.28 (s, 6H, methyl protons). ^{13}C NMR (D_2O, 100 MHz): δ 127.1, 74.9, 56.1 EI-HR-MS (positive mode): calcd 98.0964 for $C_6H_{12}N$ ([M − Cl]$^+$), found 98.0970. Anal. Calcd for C_6H_{12}NCl: C, 53.93; H, 9.05; N, 10.48. Found: C, 53.71; H, 9.07; N, 10.30.

Compound 6.[4] The compound was synthesized by the following method:



In a 200 mL flask, allylamine (0.566 g, 9.92 mmol) and triethylamine (1.00 g, 9.92 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled with an ice bath. 2-Nitrobenzenesulfonyl chloride (2.00 g, 9.02 mmol)[20] was added dropwise over 5 min, and the solution was stirred at room temperature for 30 min. After the reaction mixture was quenched with aqueous HCl (1 M, 20 mL), the organic phase was separated. The solvent was evaporated, and the residue was dissolved in AcOEt and washed with water. The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The evaporation of the solvent gave compound **10** as a colorless oil (1.65 g, 76% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14−8.12 (m, 1H, 3-Ph), 7.88−7.85 (m, 1H, 4-Ph), 7.77−7.73 (m, 2H, 5-Ph and 6-Ph), 5.73 (m, 1H, −CH═CH$_2$), 5.43 (br, 1H, −SO$_2$NH−), 5.23−5.18 (m, 1H, −CH═CH_α), 5.13−5.09 (m, 1H, −CH═CH_β), 3.77 (m, 2H, −NCH_2CH═CH$_2$).

Compound **10** (1.65 g, 6.80 mmol) obtained above was dissolved in DMF (10 mL) in a 100 mL flask equipped with a condenser. After

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K_2CO_3 (2.80 g, 20.4 mmol) and 4-bromo-1-butene (1.00 g, 7.50 mmol) were added, the solution was stirred at 60 °C under a N_2 atmosphere. After 1 h, 4-bromo-1-butene was further added (0.50 g, 3.75 mmol) and the solution was stirred at 60 °C for 30 min. The solution was cooled to room temperature, and water (50 mL) was added before extraction with ether (three times). The ether phases were combined and dried over Na_2SO_4. The solvent was evaporated, and the red residue was subjected to silica gel column chromatography with hexane/AcOEt = 2/1 as eluent to give compound **11** as a pale yellow oil (1.74 g, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, J = 6.8 Hz, 1H, 3-Ph), 7.72−7.62 (m, 3H, 4-Ph, 5-Ph, and 6-Ph), 5.70 (m, 2H, $-CH{=}CH_2 \times 2$), 5.21 (m, 2H, $-NCH_2CH{=}CH_2$), 5.02 (m, 2H, $-NCH_2CH_2CH{=}CH_2$), 3.96 (d, 2H, J = 7.0 Hz, $-NCH_2CH{=}CH_2$), 3.36 (dd, J = 7.5 Hz, 7.5 Hz, 2H, $-NCH_2CH_2CH{=}CH_2$), 2.29 (dd, J = 7.5 Hz, 7.5 Hz, 2H, $-NCH_2CH_2CH{=}CH_2$). ^{13}C NMR (D_2O, 100 MHz): δ 135.6, 130.0, 126.4, 121.6, 52.1, 48.5, 32.7. EI-HR-MS (positive mode): calcd 112.1121 for $C_7H_{14}N$ ($[M - Cl]^+$), found 112.1133.

In a 100 mL two-neck flask equipped with a condenser, *p*-toluenethiol (1.83 g, 14.8 mmol) was dissolved in MeCN (5 mL) and cooled with an ice bath. To the solution was added 11 M aqueous KOH (1.4 mL) over 10 min, and the solution was stirred for 5 min. Compound **11** (1.74 g, 5.9 mmol) in MeCN (5 mL) was slowly added to the aforementioned solution over 20 min before the solution was stirred at 50 °C for 1 h. After the disappearance of **11** was confirmed by TLC, aqueous HCl (1 M) was added to extract the deprotected amine. The water phase was brought out to pH 12 by adding aqueous KOH. The amine was extracted with CH_2Cl_2 three times to remove excess *p*-toluenethiol, and the organic phase was dried over Na_2SO_4. After filtration, the solution was cooled with an ice bath. To the solution was added di-*tert*-butyl dicarbonate (1.54 g, 7.10 mmol). The reaction mixture was stirred at room temperature for 1 h, washed with water, and dried over Na_2SO_4. The solvent was evaporated to yield a colorless oil. The oil was dissolved in 4 M HCl in dioxane, and the solution was stirred at room temperature for 18 h. After the solvent was evaporated, the residue was triturated with ether to yield a white solid. The solid was collected by suction, rinsed with ether, and dried in vacuo. Compound **6** (0.540 g) was obtained in a yield of 62% in three steps from **12**. ^{1}H NMR (D_2O, 400 MHz): δ 5.90 (m, 1H, $-NCH_2CH{=}CH_2$), 5.81 (m, 1H, $-NCH_2CH_2CH{=}CH_2$), 5.49 (m, 2H, $-NCH_2CH{=}CH_2$), 5.22 (m, 2H, $-NCH_2CH_2CH{=}CH_2$), 3.66 (d, 2H, J = 6.8 Hz, $-NCH_2CH{=}CH_2$), 3.14 (t, 2H, J = 7.1 Hz, $-NCH_2CH_2CH{=}CH_2$), 2.46 (td, 2H, J = 7.1 Hz, 6.9 Hz, $-NCH_2CH_2CH{=}CH_2$). ^{13}C NMR (D_2O, 100 MHz): δ 135.6, 130.0, 126.4, 121.6, 52.1, 48.5, 32.7. EI-HR-MS (positive mode): calcd 112.1121 for $C_7H_{14}N$ ($[M - Cl]^+$), found 112.1133. Anal. Calcd for $C_7H_{14}NCl$: C, 56.94; H, 9.56; N, 9.49. Found: C, 56.76; H, 9.48; N, 9.52.

Spectroscopic Data of RCM Product from 6 (6-RCM). ^{1}H NMR (D_2O, 400 MHz): δ 5.99 (m, 1H, $-NCH_2CH_2CH{=}CHCH_2N-$), 5.77 (m, 1H, $-NCH_2CH_2CH{=}CHCH_2N-$), 3.68 (dt, 2H, J = 2.6 Hz, 5.5 Hz, $-CH{=}CHCH_2N-$), 3.34 (t, 2H, J = 6.3 Hz, $-NCH_2CH_2CH{=}CH-$), 2.40 (m, 2H, $-NCH_2CH_2CH{=}CH-$). ^{13}C NMR (D_2O, 100 MHz): δ 128.3, 122.3, 44.4, 43.4, 23.8.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR data of substrates and authentic samples of products, ^{1}H NMR spectra of reaction mixtures, UV−vis spectra, and ESI-TOF-MS spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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