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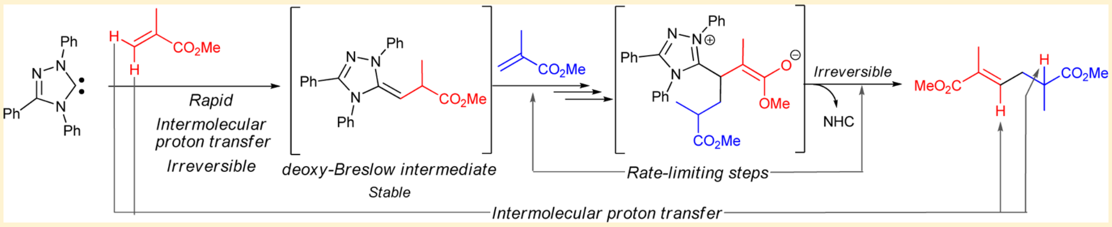
Experimental Mechanistic Studies of the Tail-to-Tail Dimerization of Methyl Methacrylate Catalyzed by N-Heterocyclic Carbene

Terumasa Kato, Yoshiya Ota, Shin-ichi Matsuoka,* Koji Takagi, and Masato Suzuki

Department of Materials Science and Engineering, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya, Aichi 466-8555, Japan

Ⓢ *Supporting Information*



ABSTRACT: We and others have previously reported the intermolecular umpolung reactions of Michael acceptors catalyzed by an N-heterocyclic carbene (NHC). The representative tail-to-tail dimerization of methyl methacrylate (MMA) has now been intensively investigated, leading to the following conclusions: (1) The catalysis involves the deoxy-Breslow intermediate, which is quite stable and remains active after the catalysis. (2) Addition of the intermediate to MMA and the final catalyst elimination are the rate-limiting steps. Addition of the NHC to MMA and the proton transfers are relatively very rapid. (3) The two alkenyl protons of the first MMA undergo an intermolecular transfer to C3 and C5 of the dimer. (4) The initial proton transfer is intermolecular. (5) Compared with the benzoin condensation, noticeable differences in the kinetics, reversibility, and stability of the intermediates are observed.

■ INTRODUCTION

Umpolung or polarity reversal of functional groups is an important concept in the design of synthetic strategies. Recently, the N-heterocyclic carbene[1] (NHC)-catalyzed umpolungs of aldehydes have been well-explored,[2] thereby allowing a variety of bond-forming reactions of aldehydes with electrophiles, including asymmetric syntheses. The beginning of this type of reaction, in fact, dates back half a century. Ukai reported the first benzoin condensation catalyzed by thiamine in 1943,[3] and Breslow proposed a reaction mechanism involving an enaminol intermediate (the Breslow intermediate) in 1958 (Scheme 1a).[4] In addition to the homocouplings, Stetter described the selective cross-coupling between aldehydes and Michael acceptors via Breslow intermediates.[5] Since these initial reports, significant efforts have been directed toward mechanistic studies, including kinetics,[6] analysis and isolation of the intermediate,[7] effects of the catalyst[8] and additives,[9] and theoretical considerations.[10] These fundamental studies have advanced the recent development of NHC catalysis and are still in progress.

In addition to aldehydes, the NHC-catalyzed umpolung of Michael acceptors has also become possible. The first publication appeared in 2006, showing an intramolecular S_N2 reaction of deoxy-Breslow intermediates.[11] Subsequently, this interesting reactivity was computationally studied by comparison with the Me_3P-catalyzed Morita–Baylis–Hillman-like reaction.[12] In 2011, we and others independently reported NHC-catalyzed intermolecular umpolung reactions involving tail-to-tail dimerization of activated olefins (Scheme 1b).[13,14] These are analogues of the benzoin condensation and provide facile access to useful difunctional compounds. The other umpolung reactions, such as the rearrangement[15] or Rauhut–Currier reactions[16] of vinyl sulfones and three-component reactions using isocyanates,[17] have also been reported. The key deoxy-Breslow intermediate derived from an imidazolium-based NHC and methyl methacrylate (MMA) was isolated and structurally characterized.[18] The intermediates can also be formed from NHCs and alkyl halides,[19] and importantly, their nucleophilic reactivities have been disclosed.[20] In contrast to aldehydes, however, the NHC-catalyzed umpolung of other electrophiles is largely underdeveloped. In view of the fact that there is no other general procedure to introduce electrophiles at the β-carbon of Michael acceptors, their NHC-catalyzed umpolungs are particularly promising. However, the reaction scope and catalytic activity still remain low. To overcome such difficulties, fundamental mechanistic studies are required. We have now experimentally investigated a representative intermolecular umpolung reaction of a Michael acceptor catalyzed by an NHC, namely, the tail-to-tail dimerization of MMA,[21] to understand the reversibility, rate-limiting step, and proton-transfer mechanism. In addition, we have compared the mechanism of this reaction with that of the benzoin condensation.

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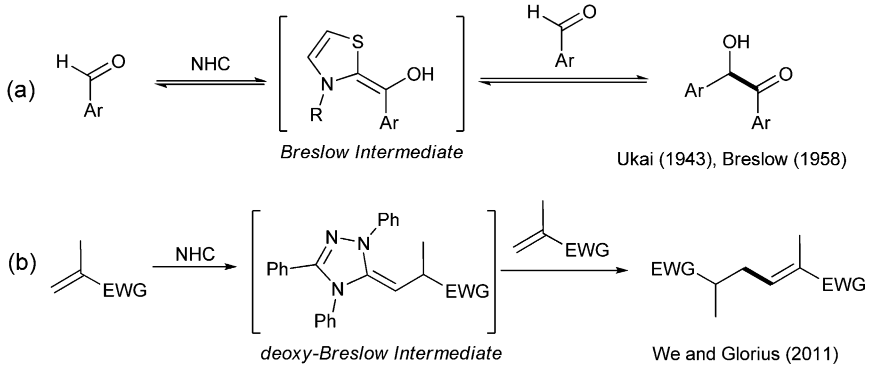
Scheme 1. NHC-Catalyzed Umpolung Reactions: (a) Benzoin Condensation; (b) Tail-to-Tail Dimerization of Activated Olefins



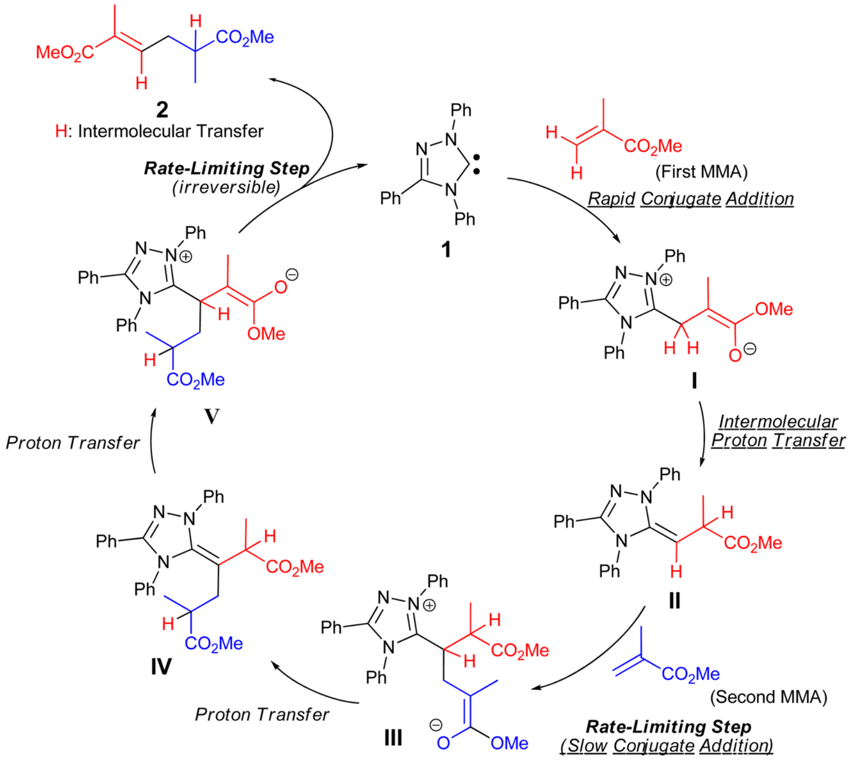
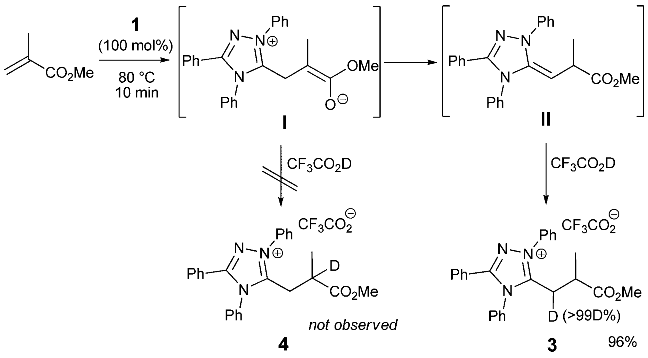


Figure 1. Reaction mechanism for the tail-to-tail dimerization of MMA catalyzed by NHC **1**.

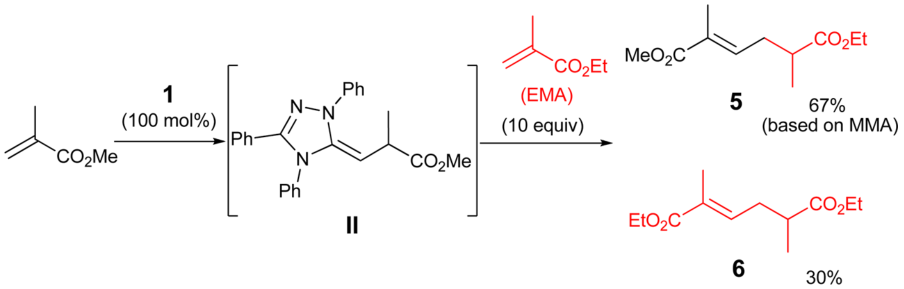
RESULTS AND DISCUSSION

Deoxy-Breslow Intermediate and Rate-Limiting Steps. We previously reported that the intermediates **II** and **IV** (Figure 1) were detected by ESI-MS,[13] and we[17] and Glorius and co-workers[14] obtained the proton adducts of **II**. On the basis of these results, the catalytic cycle shown in Figure 1 was proposed. We initially investigated the detailed mechanistic aspects of the first half of the catalytic cycle (**1** → **II**). When the reaction of MMA with an equimolar amount of **1** for 10 min was quenched by CF_3CO_2D, compound **3** with selective deuterium incorporation at the β-carbon was obtained in 96% yield without the formation of **4** (Scheme 2). This experiment indicated that the proton transfer of the ester enolate **I** rapidly proceeds to generate relatively stable species **II**. In addition, the in situ generation of **II** supports the fact that this catalysis involves the umpolung at the β-carbon. The selective generation of **II** enables the stoichiometric codimerization. As expected, the reaction of **II** with ethyl methacrylate (EMA) produced codimer **5**, and the regenerated **1** catalyzed the dimerization of the excess amount of EMA to give **6** (Scheme 3). The MMA dimer **2** was not formed, suggesting that the reaction step **1** → **II** is apparently irreversible under these conditions.

Scheme 2. Deuterium Labeling of in-Situ Generated II Using CF_3CO_2D



Scheme 3. Stoichiometric Codimerization of MMA with EMA



Scheme 4. Codimerization of MMA and EMA To Examine the Activities of Intermediates II and IV

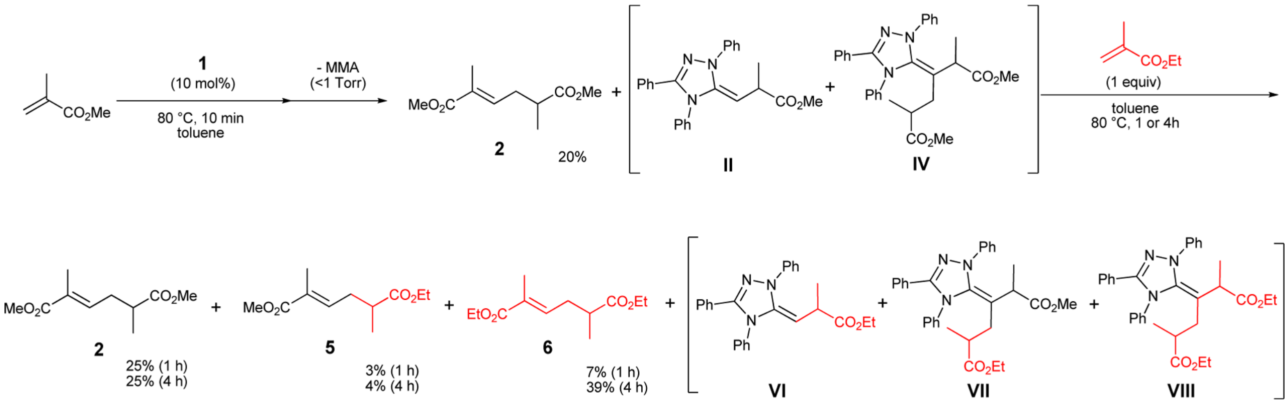
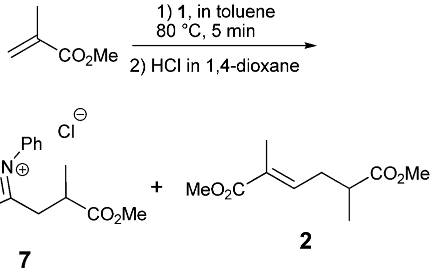


Table 1. Reactions of MMA with 1 for 5 min



			yield (%)	
entry	[1] mol %	conv. (%)[a]	7[b]	2[a]
1	100	83	77	0
2	50	51	45	0
3	10	13	9	1

[a]Determined by GC. [b]Isolated yields.

Although the isolation of intermediary species derived from **1** and two molecules of MMA has been unsuccessful, compound **IV** would be a stable intermediate capable of being detected by ESI-MS. Throughout the catalysis, only **II** and **IV** were detected by ESI-MS, and no intermediary adducts derived from trimers and tetramers were observed. To examine the activities of the in situ-generated **II** and **IV**, the codimerization was performed as shown in Scheme 4. The dimerization of MMA with 10 mol % **1** for 10 min gave the dimer **2** in 20% GC yield. NHC **1** was completely consumed, and **II** and **IV** were detected by ESI-MS. Subsequently, the unreacted MMA was excluded in vacuo, and then the mixture was reacted with an equimolar amount of EMA for 1 or 4 h to give dimers **2, 5,** and **6** and intermediates **VI, VII,** and **VIII.** During this second stage, the yield of **2** increased from 20% to 25% as a result of the elimination of **2** from **IV.** Codimer **5** was produced in yields of 3 and 4% by the reaction of **II** and EMA for 1 and 4 h, respectively. These processes regenerated **1,** which subsequently catalyzed the dimerization of EMA to give **6** in yields of 7 and 39%. Collectively, the active intermediates **II** and **IV** are quite stable during the catalysis and would be involved in the rate-limiting steps.

We then studied the short-time reactions of MMA with **1** (100, 50, and 10 mol %). The reactions were quenched after 5 min by the addition of HCl (Table 1). In all cases, the conversions of MMA were almost consistent with the yields of the HCl adduct of **II** (**7**). The absence of further reaction of **II** with a large amount of unreacted MMA is particularly noteworthy (entry 3). The time−conversion plot for the catalysis also suggests a higher rate for the conjugate addition of **1** to MMA (Figure S17 in the Supporting Information). Under the conditions of entry 3 in Table 1, the conversion reached 10% within 3 min, and then the reaction proceeded much more slowly. Therefore, the reaction of **1** with MMA to form **II** is much more rapid than the subsequent conjugate addition of **II** to MMA.

The deuterium kinetic isotope effect using MMA-d_8 was next examined. The time−yield plots for the dimerizations of MMA and MMA-d_8 show that the yields at the initial stage increased linearly with the reaction time without an induction period (Figures S18−S22 in the Supporting Information). As shown in Table 2, the rate of the dimerization of MMA-d_8 was slightly higher than that of MMA ($k_{\mathrm{H}}/k_{\mathrm{D}} = 0.81 \pm 0.13$), suggesting an inverse secondary deuterium kinetic isotope effect. When the competitive dimerization using an equimolar mixture of MMA and MMA-d_8 was performed (Figure 2), GC analysis of the product showed three peaks assignable to the two homodimers (25% GC yield each) and the codimer (50% GC yield). The relative intensity among the three peaks was a constant 1:2:1

Table 2. Kinetic Isotope Effect in the Dimerizations of MMA and MMA-d_8[a]

entry	substrate	dimerization rate (10^{-4} mol L^{-1} s^{-1})[b]
1	MMA	1.17
2	MMA	1.06
3	MMA	1.15
4	MMA-d_8	1.24
5	MMA-d_8	1.53

[a] 10 mol % of **1**, 3.0 mmol of substrate, 0.70 mL of toluene, at 80 °C. [b] Initial stage of the reactions (yield <12%). Caluculated by GC.

throughout the catalysis (Figure 2a). This result also supports the conclusion that the reactivities of the two substrates are similar and that there is no primary deuterium kinetic isotope effect. Accordingly, all three proton-transfer processes in the catalysis are relatively very rapid, and it is reasonable to assume that the proton transfers in the second half of the catalytic cycle (**III** → **IV** and **IV** → **V**) are faster than the final elimination step (**V** → **1**). Collectively, we propose that the conjugate addition of **II** to MMA (**II** → **III**) and the final elimination of **1** (**V** → **1**) are partially rate-limiting. In addition, this final step is irreversible, as no reaction of **1** with **2** occurs at all.

Proton-Transfer Mechanism. In the competitive dimerization, 11 signals corresponding to the Na^+ adducts of the homo- and codimers were observed in the ESI-MS spectrum (Figure 2b). The MMA dimer showed three isotope signals at *m/z* 223, 224, and 225 with the statistical intensity ratio of 1:2:1. A similar splitting of signals was observed for the dimer of MMA-d_8. These results indicate that two intermolecular H/D exchanges can take place for two protons or deuteriums during the catalysis. The dimerization of MMA in the presence of 1.3 equiv of CD_3OD produced dimer **9** with deuterium incorporation at C3 and C5, accompanied by the trans-esterification (Scheme 5). Since no H/D exchange occurs at C3 and C5 of **2** under these conditions, intermolecular transfers of these two protons are involved during the catalysis.

The initial proton transfer (**I** → **II**) was examined next. The reaction of in situ-generated **II** with an excess amount of CD_3OD at room temperature followed by the addition of HCl gave **10**, indicating that H/D exchange at the *β*-carbon of **II** takes place (Scheme 6). Compound **11** with deuterium incorporation at the *α*-carbon, which would be produced via intermediate **I**, was not formed, suggesting that there is no equilibrium between **I** and **II** under these conditions. To further examine the proton transfer of **I** to form **II**, we performed the reaction of the mixture of MMA and MMA-d_8 with a stoichiometric amount of **1** (Scheme 7). ESI-MS analysis of the reaction mixture quenched with HCl indicated the presence of not only **7** but also H/D-exchanged intermediates such as **11**. In addition, the stoichiometric reaction of MMA with **1** in the presence of an excess of CD_3OD led to deuterium incorporation at the *α*- and *β*-carbons to give **12** (Scheme 8). Since **II** does not undergo the H/D exchange reaction at the *α*-carbon under these conditions (Scheme 6), intermediate **I** reacts with CD_3OD, leading to the deuterium incorporation at the *α*-carbon in **12**. On the basis of the results shown in Schemes 6–8, we postulate that the proton-transfer process from **I** to **II** is intermolecular.

To reveal the proton-transfer mechanism of the second half of the catalytic cycle (**II** → **1**), deuterium-labeling experiments involving the stoichiometric dimerizations were performed (Schemes 9 and 10). The reaction of **II** with MMA-d_8 produced codimer **13** deuterated at C4 accompanied by the formation of MMA-d_8 dimer **8** and isomers of the deuterated dimers (Scheme 9). When intermediate **IX** (prepared as shown in

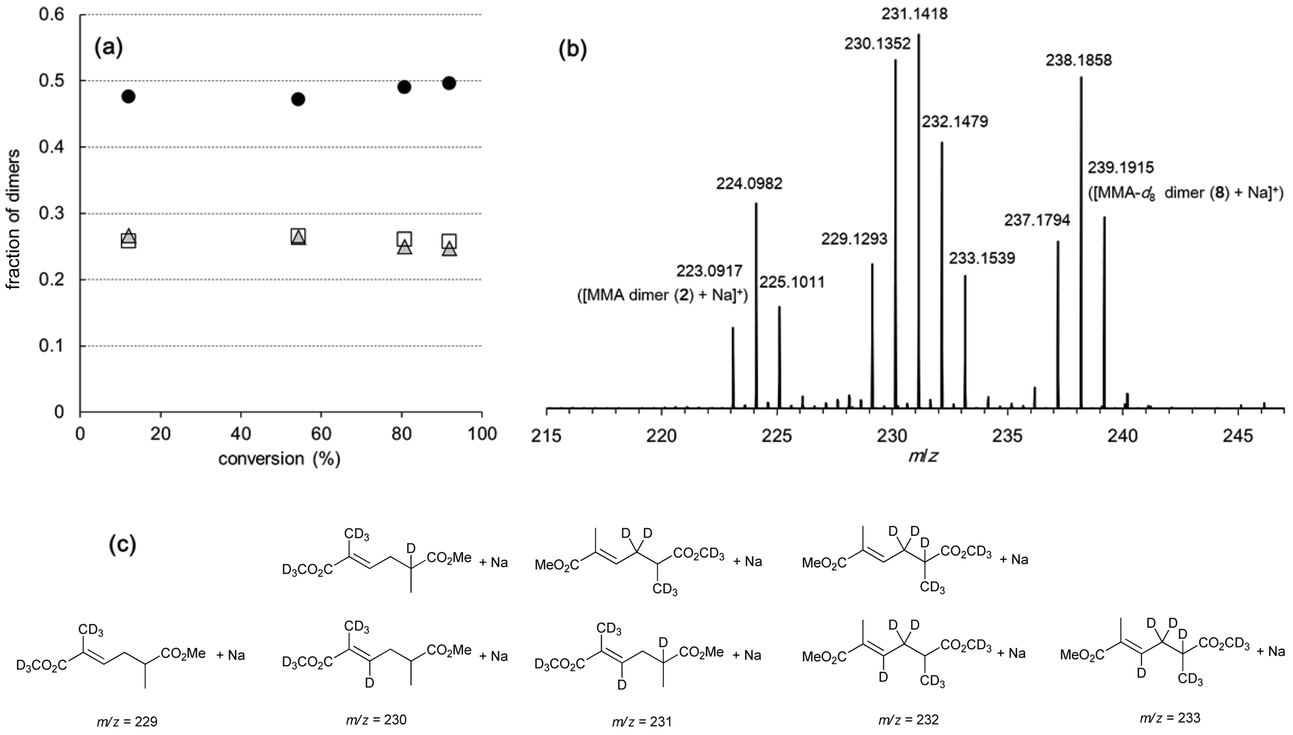
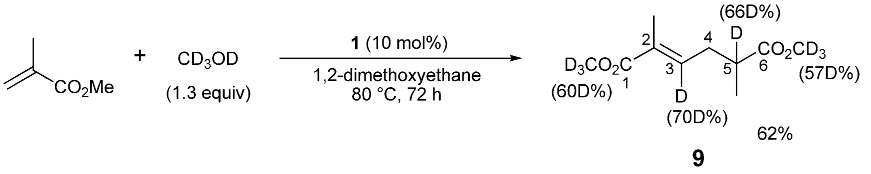
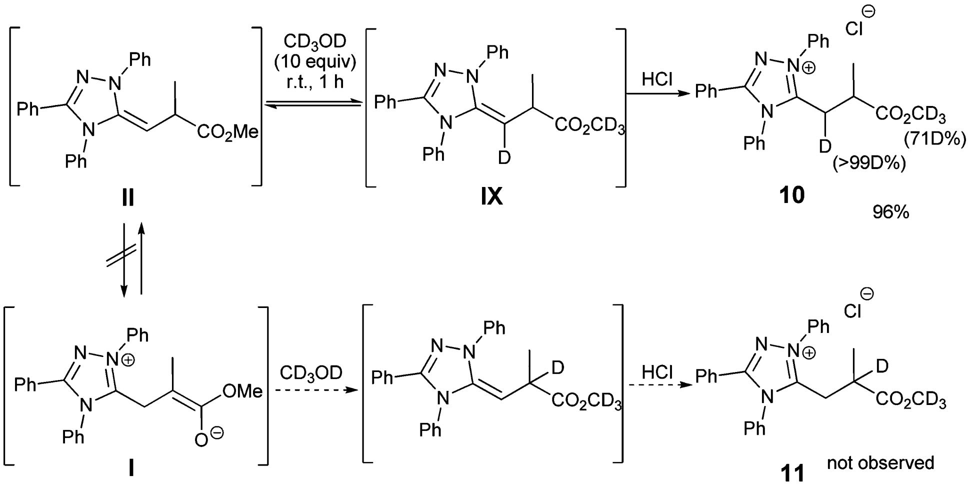


Figure 2. Dimerization of the mixture of MMA and MMA-d_8 catalyzed by **1** in toluene at 80 °C for 8 h. (a) Fractions of the dimers vs conversion: ●, codimer; □, MMA dimer; △; MMA-d_8 dimer. The fractions were estimated by GC. (b) ESI-MS spectrum of the obtained dimers. (c) Assignment of signals (*m/z* 229–233) observed in the ESI-MS spectrum.

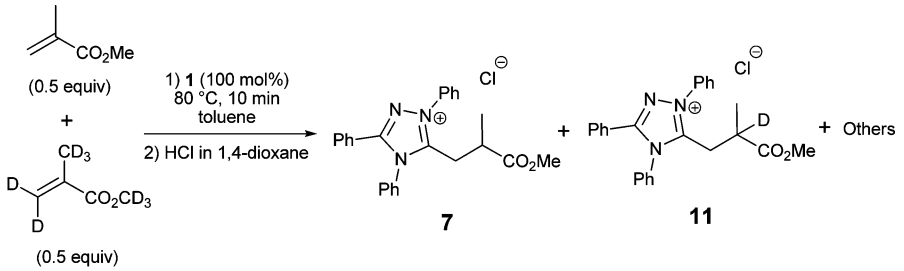
Scheme 5. Dimerization of MMA in the Presence of CD_3OD



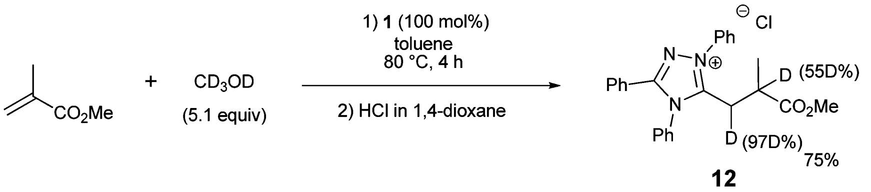
Scheme 6. H/D Exchange Reaction of the β-Carbon of II in the Presence of CD_3OD



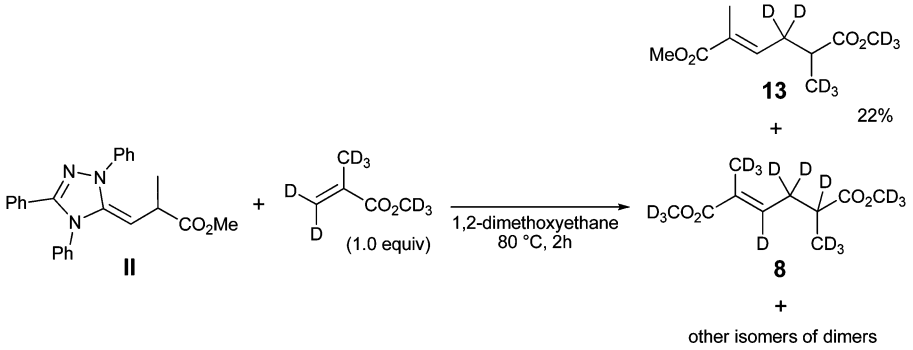
Scheme 7. Reaction of the Mixture of MMA and MMA-d_8 with 1



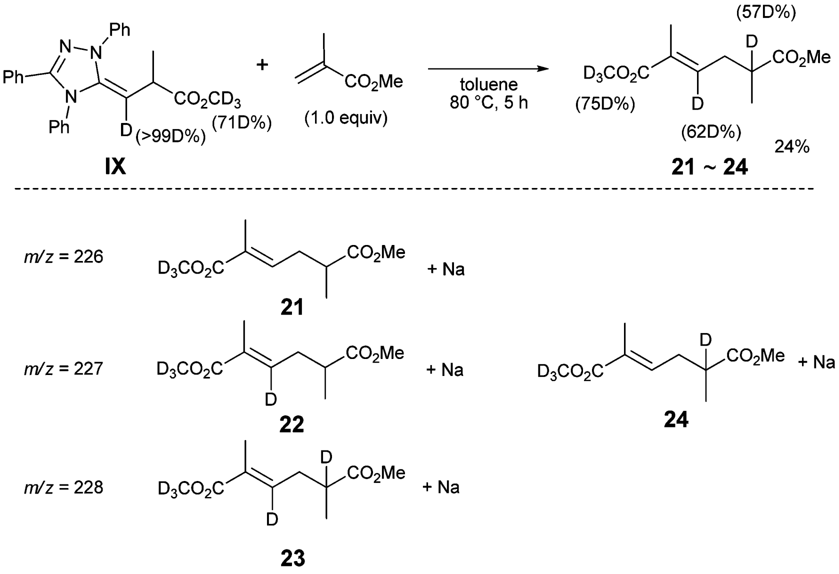
Scheme 8. Reaction of MMA with 1 in the Presence of CD_3OD



Scheme 9. Reaction of II with MMA-d_8



Scheme 10. Reaction of IX with MMA



Scheme 6) was reacted with MMA, the dimer deuterated at C3 and C5 was obtained with moderate deuterium incorporations (Scheme 10). The ESI-MS spectrum of the product showed three signals at *m*/*z* 226, 227, and 228 with the statistical intensity ratio of 1:2:1, corresponding to dimers **21, 22, 23**, and **24**. These results indicate that the *α*- and *β*-protons of **II** undergo intermolecular scrambling and transfer to C3 and C5 of **2**.

Collectively, the alkenyl protons of the first MMA are transferred to C3 and C5 of the dimer, while the transfer of the protons of the second MMA does not take place at all. The first proton-transfer step (**I** → **II**) is intermolecular, and the second (**III** → **IV**) and third (**IV** → **V**) steps involve complex intermolecular transfer processes. This finding agrees well with the result of the competitive dimerization (Figure 2). As shown in Figure 2b, the five isotope codimers were observed at *m*/*z* 229−233 with the statistical intensity ratio of 1:2:2:2:1. On the basis of the proton-transfer mechanisms, the structures of the eight isotope codimers can be reasonably assigned as shown in Figure 2c.

Comparison with Benzoin Condensation. The dimerization of MMA is analogous to the benzoin condensation, as both reactions involve an NHC-catalyzed umpolung for bond formation between a couple of electrophilic unsaturated carbons to produce a dimer. The mechanism of the benzoin condensation, including the rate-limiting steps, proton-transfer process, and reversibility, have been accepted (Scheme 11). Although there are a few examples showing that the initial proton transfer to generate the Breslow intermediate is irreversible, depending on the catalyst used,[6e,8e,f] it is generally accepted that the overall benzoin condensation is reversible.[5,22] Previous reports have demonstrated that no significant difference in the rate-limiting steps of the benzoin condensation is observed between the experimental and theoretical studies using a thiazolium-based catalyst[6d] and a triazolium variant,[10g] respectively, showing that the initial addition (**X** → **XI**), the initial proton transfer (**XI** → **XII**), and the C−C bond formation (**XII** → **XIII**) are partially rate-limiting. The differences and similarities between these two reactions are summarized in Table 3. In contrast to the benzoin condensation, the **1** → **II** and **V** → **1** steps in the dimerization of MMA are apparently irreversible, the initial addition (**1** → **I**) and the initial proton transfer (**I**→**II**) are relatively fast, and the rates of the final eliminations of the catalysts (**V** → **1**) are relatively slow. Similar to the benzoin condensation, the initial proton transfer (**I** → **II**) is intermolecular, and the addition of **II** to MMA is partially rate-limiting. Efforts have been directed toward the isolation and characterization of the Breslow intermediates, but successful examples are very limited. In contrast, the isolation of the deoxy-Breslow intermediate derived from the imidazolium-based NHC and MMA was previously reported,[18] and the selective generation of **II** has

Scheme 11. NHC-Catalyzed Benzoin Condensation

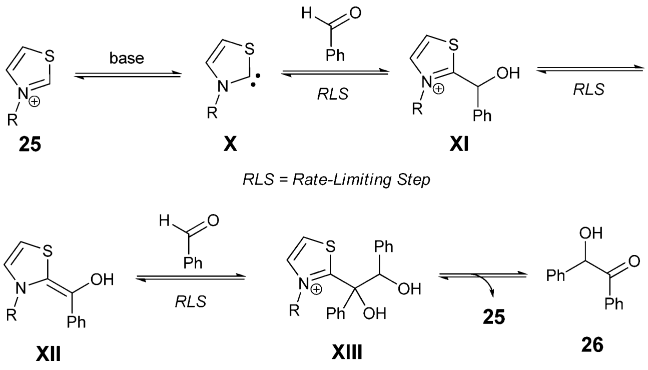


Table 3. Comparison of the Dimerization of MMA and the Benzoin Condensation

	dimerization of MMA	benzoin condensation[a]
initial addition	**1** → **I**: fast	**X** → **XI**: slow
initial proton transfer	**I** → **II**: fast, intermolecular	**XI** → **XII**: slow, intermolecular
intermediate	**II**: stable	**XII**: unstable
	II → **1**: irreversible	**XII** → **25**: reversible
	II → **III**: slow	**XII** → **XIII**: slow
elimination	**V** → **1**: slow	**XIII** → **25**: fast
product	**2** → **V**: irreversible	**26** → **XII**: reversible

[a]See refs 6d and 10g.

been established. Thus, the deoxy-Breslow intermediates are much more stable than the Breslow variants.

■ CONCLUSIONS

We have reported detailed experimental mechanistic studies of the NHC-catalyzed dimerization of MMA. A series of experiments, including kinetic isotope effects, competitive reactions, deuterium-labeling studies, reactions of the intermediates, and codimerizations have been performed to reveal the rate-limiting steps, proton-transfer process, and reversibility. NHC **1** rapidly adds to the first MMA to generate **I**, and this is followed by an intermolecular proton transfer to give the key deoxy-Breslow intermediate **II**. This process is apparently irreversible, and **II** is selectively generated in situ, thereby allowing the stoichiometric codimerizations. The addition of **II** to the second MMA to form the C−C bond is partially rate-limiting. The final electron transfer to produce **2** is irreversible and also partially rate-limiting. All of the proton transfers are relatively very rapid, and the k_H/k_D value of 0.81 ± 0.13 suggests an inverse secondary deuterium isotope effect. The alkenyl protons of the first MMA are transferred to C3 and C5 of **2** through an intermolecular exchange. We have summarized the similarities and differences between this dimerization and the benzoin condensation in regard to the kinetics, reversibility, and stability of the intermediates. This fundamental study can provide opportunities for the discovery of new NHC-catalyzed umpolung reactions. Further studies along this line are now in progress in our laboratory.

■ EXPERIMENTAL SECTION

General. All of the reactions were performed under a nitrogen atmosphere using standard Schlenk techniques. MMA, EMA, and 1,2-dimethoxyethane were distilled from CaH_2 under reduced pressure before use. Other chemicals were used as received. MMA-d_8 (98.8 atom % D) was purchased from a commercial supplier. The GC yields and conversions were estimated using *n*-dodecane as an internal standard. Purification by Kugelrohr distillation under reduced pressure (<1 Torr) at 110 °C for **2** or 135 °C for **6** gave dimers as transparent liquids. The deoxy-Breslow intermediates could be purified by silica gel column chromatography using CH_2Cl_2/MeOH as the eluent, but this purification caused an undesired H/D exchange reaction at the *β*-carbon. The ESI-MS measurements on the deuterated intermediates also resulted in H/D exchange. NMR spectra were recorded on spectrometers at 600, 500, and 400 MHz. Chemical shifts were expressed relative to tetramethylsilane (0.0 ppm) for ^1H and the $CDCl_3$ resonance (77.1 ppm) for ^{13}C. The NMR peak assignments of the dimers and the deoxy-Breslow intermediates were performed using COSY, HMQC, and DEPT135 measurements. ESI-MS was performed using a quadrupole orthogonal acceleration time-of-flight instrument equipped with a Z-spray nanoelectrospray ionization source. GC analysis was performed on an instrument equipped with a flame ionization detector and a fused silica capillary column (30 m × 0.25 mm i.d. × 0.25 μm film thickness). All of the dimers were also characterized by GC.

Deuterium-Labeling Experiment of II (Scheme 2). To a solution of **1** (89 mg, 0.30 mmol) in 1,2-dimethoxyethane (0.6 mL) was added MMA (30 mg, 0.30 mmol) at 80 °C. After the mixture was stirred for 10 min, CF_3CO_2D (0.14 g, 1.23 mmol) was added, and stirring was continued for 1 h. The reaction mixture was filtered through a Celite pad and dried in vacuo to give **3** as a yellow liquid in 96% crude yield (0.15 g, 0.29 mmol). ^1H NMR (600 MHz, $CDCl_3$) δ: 1.04 (3H, d, *J* = 7.0 Hz), 2.27 (1H, brs), 3.10 (0.48H, brs), 3.57 (3H, s), 3.70 (0.48H, brs). 7.35−8.01 (15H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.9, 160.9, 160.5, 160.1, 159.7, 120.0−134.7, 120.0, 117.2, 114.3, 111.4, 52.5, 35.7, 35.6, 28.2, 16.9.

Stoichiometric Codimerization of MMA and EMA (Scheme 3). To a solution of **1** (89 mg, 0.30 mmol) in 1,2-dimethoxyethane (0.6 mL) was added MMA (27 mg, 0.27 mmol) at 80 °C. After the mixture was stirred for 1 h, EMA (0.34 g, 3.0 mmol) was added, and stirring was continued for 4 h. Kugelrohr distillation under reduced pressure gave 0.14 g of a mixture of **5** (0.18 mmol, 67% ^1H NMR yield based on MMA) and **6** (0.45 mmol, 30% ^1H NMR yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18−1.31 (9.2H), 1.85 (3.1H), 2.29−2.36 (1.0H), 2.50−2.61 (2.1H), 3.74 (0.87H), 4.11−4.21 (3.8H), 6.69−6.72 (1.0H). HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{18}O_4Na$ $[\mathbf{5} + Na]^+$ 237.1103, found 237.1104; calcd for $C_{12}H_{20}O_4Na$ $[\mathbf{6} + Na]^+$ 251.1259, found 251.1264.

Codimerization of MMA and EMA (Scheme 4). To a solution of **1** (0.89 mg, 0.30 mmol) in toluene (0.7 mL) was added MMA (0.30 g, 3.0 mmol) at 80 °C. After the mixture was stirred for 1 h, the volatiles were evaporated under reduced pressure at room temperature. A toluene solution of *n*-dodecane (0.13 mol/L, 0.7 mL) was added, and a small aliquot was sampled and subjected to GC and ESI-MS analyses. To the mixture, EMA (0.34 g, 3.0 mmol) and toluene (0.7 mL) were added. After the mixture was stirred at 80 °C for 4 h, a small aliquot of the mixture was subjected to GC and ESI-MS analyses. Kugelrohr distillation under reduced pressure gave 0.22 g of a mixture of dimers of **2**, **5**, and **6** in 25, 4, and 39% yield, respectively. The yields of the dimers were estimated by ^1H NMR and GC analyses, and the intermediates **VI**, **VII**, and **VIII** were detected by ESI-MS. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18−1.31 (7.5H), 1.85 (3.1H), 2.29−2.36 (1.0H), 2.50−2.62 (2.1H), 3.69 (1.1H), 3.74 (1.4H), 4.11−4.21 (2.7H), 6.69−6.72 (1.0H). HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{26}N_3O_2$ $[\mathbf{VI} + H]^+$ 412.2025, found 412.2027; calcd for $C_{31}H_{34}N_3O_4$ $[\mathbf{VII} + H]^+$ 512.2549, found 512.2550; calcd for $C_{32}H_{36}N_3O_4$ $[\mathbf{VIII} + H]^+$ 526.2706, found 526.2714.

Reaction of MMA with 1 for 5 min (Table 1, Entry 1). To a solution of **1** (89 mg, 0.3 mmol) in toluene (0.6 mL) at 80 °C was added a solution of MMA (30 mg, 0.3 mmol) and *n*-dodecane in toluene (0.13 mol/L, 0.3 mL) at 80 °C. The reaction mixture was stirred for 5 min and then quenched with HCl in 1,4-dioxane (0.2 mL, 3.0 mol/L). A small aliquot was sampled and subjected to GC analysis to estimate the yield of **2** (0%). The crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH as the eluent to give **7** (0.10 g, 0.23 mmol) in 77% isolated yield. For the ^1H and ^{13}C NMR, HRMS, and IR data of **7**, see ref 17.

Kinetics of the Dimerizations (Table 2). To a solution of **1** (89 mg, 0.30 mmol) and *n*-dodecane (0.09 mmol) in toluene (0.70 mL) at 80 °C was added MMA (0.3 g, 3.0 mmol) at 80 °C. Aliquots were sampled from the reaction mixture at various times for 30 min and then subjected to GC analysis to estimate the yield of **2**. The reaction rate was estimated as the slope of the time−yield plot at less than 12% yield.

Competitive Dimerization of MMA and MMA-d_8 (Figure 2). To a solution of **1** (0.13 g, 0.44 mmol) in toluene (0.89 mL) were added MMA (0.22 g, 2.2 mmol) and MMA-d_8 (0.24 g, 2.2 mmol) at room temperature. The temperature was increased to 80 °C, and the mixture was stirred for 8 h. Kugelrohr distillation under reduced pressure gave 0.37 g of a mixture of the dimers in 75% yield. HRMS (ESI) *m*/*z*: calcd for $C_{10}H_{16}O_4Na$ 223.0946, found 223.0943; calcd for $C_{10}H_{15}DO_4Na$ 224.1009, found 224.1002; calcd for $C_{10}H_{14}D_2O_4Na$ 225.1072, found 225.1065; calcd for $C_{10}H_{10}D_6O_4Na$ 229.1323, found 229.1320; calcd for $C_{10}H_9D_7O_4Na$ 230.1386, found 230.1379; calcd for $C_{10}H_8D_8O_4Na$ 231.1448, found 231.1448; calcd for $C_{10}H_7D_9O_4Na$ 232.1511, found 232.1506; calcd for $C_{10}H_6D_{10}O_4Na$ 233.1574, found 233.1566; calcd for $C_{10}H_2D_{14}O_4Na$ 237.1825, found 237.1822; calcd for $C_{10}HD_{15}O_4Na$ 238.1888, found 238.1882; calcd for $C_{10}D_{16}O_4Na$ 239.1951, found 239.1940.

Dimerization of MMA in the Presence of CD_3OD (Scheme 5). To a solution of **1** (89 mg, 0.30 mmol) in 1,2-dimethoxyethane (0.7 mL) were added CD_3OD (0.14 g, 3.9 mmol) and MMA (0.30 g, 3.0 mmol). The mixture was stirred at 80 °C for 72 h. Kugelrohr distillation under reduced pressure gave **9** in 62% yield (0.19 g, 0.93 mmol). ^1H NMR (600 MHz, $CDCl_3$) δ: 1.19 (3H, m), 1.84 (3H, s), 2.31 (1H, m), 2.53 (1H, m), 2.60 (0.3H, m), 3.67 (1.3H, s), 3.73

(1.2H, s), 6.69 (0.3H, t, J = 7.1 Hz). ^{2}H NMR (77 MHz, $CHCl_3$) δ: 2.56 (1.1D), 3.63(3.2D), 3.68 (3.0D), 6.70 (1.0D). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.9, 168.3, 138.7, 138.4, 138.3, 138.2, 129.3, 129.2, 51.7, 51.1, 51.0, 50.8, 38.7, 38.5, 38.3, 38.2, 32.7, 32.4, 32.3, 32.2, 16.8, 16.7, 12.4. HRMS (ESI) m/z: calcd for $C_{10}H_8D_8O_4Na$ [**9** + Na]$^+$ 231.1448, found 231.1449.

H/D Exchange Reaction of the β-Carbon of II in the Presence of CD_3OD (Scheme 6). To a solution of **1** (89 mg, 0.30 mmol) in toluene (0.6 mL) at 80 °C was added MMA (30 mg, 0.30 mmol). After the mixture was stirred for 5 min, CD_3OD (0.11 g, 3.0 mmol) was added at room temperature, and the stirring was continued for 1 h. After the volatiles were removed under reduced pressure, CH_2Cl_2 (0.6 mL) was added, and the reaction was quenched with HCl in 1,4-dioxane (0.2 mL, 3.0 mol/L). Precipitation of the mixture into hexane gave **10** as a white solid in 96% crude yield (0.13 g, 0.29 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, d, J = 6.9 Hz), 2.27 (1H, m), 3.22 (0.48H, m), 3.54 (0.88H, s), 4.15 (0.48H, m), 7.29−8.24 (15H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 154.8−120.8, 52.4, 35.7, 35.68, 35.66, 35.60, 29.6, 17.29, 17.26, 17.24.

Reaction of the Mixture of MMA and MMA-d_8 with 1 (Scheme 7). To a solution of **1** (89 mg, 0.30 mmol) in 1,2-dimethoxyethane (0.6 mL) was added a mixture of MMA (15 mg, 0.15 mmol) and MMA-d_8 (16 mg, 0.15 mmol) in toluene (0.3 mL) at 80 °C. After the mixture was stirred for 5 min, HCl in 1,4-dioxane (0.2 mL, 3.0 mol/L) was added, and the mixture was stirred at room temperature for 1 h. The crude product was filtered through a Celite pad using CH_2Cl_2 as the eluent and dried in vacuo to give isomers of the deoxy-Breslow intermediates (80 mg, white solid). HRMS (ESI) m/z: calcd for $C_{25}H_{24}N_3O_2$ [**7** − Cl]$^+$ 398.1869, found 398.1877; calcd for $C_{25}H_{23}DN_3O_2$ [**11** − Cl]$^+$ 399.1931, found 399.1930.

Reaction of MMA with 1 in the Presence of CD_3OD (Scheme 8). To a solution of **1** (89 mg, 0.30 mmol) in toluene (0.3 mL) was added a mixture of MMA (30 mg, 0.30 mmol) and CD_3OD (55 mg, 1.53 mmol). The mixture was stirred at 80 °C for 4 h. The volatiles were removed under reduced pressure, and then CH_2Cl_2 (0.6 mL) and HCl in 1,4-dioxane (0.2 mL, 3.0 mol/L) were added. Precipitation of the mixture into hexane gave **12** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, m), 2.27 (0.45H, m), 3.22 (0.53H, m), 3.55 (3H, m), 4.10 (0.51H, m), 7.31−8.56 (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 120.8−154.9, 52.4, 35.8, 35.7, 29.7, 29.6, 17.3, 17.2.

Reaction of II with MMA-d_8 (Scheme 9). To a solution of **1** (89 mg, 0.30 mmol) in toluene (0.6 mL) was added MMA (30 mg, 0.30 mmol) at 80 °C. After the mixture was stirred for 10 min, the volatiles were evaporated under reduced pressure. 1,2-Dimethoxyethane (0.6 mL) and MMA-d_8 (32 mg, 0.30 mmol) were added, and the mixture was stirred at 80 °C for 2 h. Kugelrohr distillation under reduced pressure gave 24 mg of a mixture of **13** (22% ^{1}H NMR yield), **8**, and other isomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.85 (3H, s), 2.57 (1H, s), 3.73 (3H, s), 6.69 (1H, s). ^{2}H NMR (77 MHz, $CHCl_3$) δ: 1.15 (3.0D), 1.81 (0.8D), 2.30 (0.9D), 2.51 (1.1D), 3.65(4.0D), 6.72 (0.4D). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 168.4, 138.7, 129.5, 129.4, 51.8, 51.4, 51.1, 51.0, 38.5, 12.6, 12.5. HRMS (ESI) m/z: calcd for $C_{10}H_8D_8O_4Na$ [**13** + Na]$^+$ 231.1448, found 231.1449; calcd for $C_{10}D_{16}NaO_4$ [**8** + Na]$^+$ 239.1951, found 239.1938.

Reaction of IX with MMA (Scheme 10). To a solution of **IX** (prepared according to Scheme 6) were added toluene (0.6 mL) and MMA (30 mg, 0.30 mmol). The mixture was stirred at 80 °C for 5 h. Kugelrohr distillation under reduced pressure gave 23 mg of a mixture of dimers, **21**, **22**, **23**, and **24**. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.19 (3H, m), 1.84 (3H, s), 2.32 (1H, m), 2.53 (1H, s), 2.60 (0.43H, m), 3.68 (3H, s), 3.73 (0.74H, s), 6.69 (0.38H, m). ^{2}H NMR (61 MHz, $CHCl_3$) δ: 2.57 (0.72D), 3.69 (3.6D), 6.71 (1D). HRMS (ESI) m/z: calcd for $C_{10}H_{13}D_3O_4Na$ [**21** + Na]$^+$ 226.1135, found 226.1130; calcd for $C_{10}H_{12}D_4O_4Na$ [**22** + Na]$^+$ and [**24** + Na]$^+$ 227.1197, found 227.1194; calcd for $C_{10}H_{11}D_5O_4Na$ [**23** + Na]$^+$ 228.1260, found 228.1250.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{2}H NMR spectra; data from the kinetic study; and a GC profile. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: matsuoka.shinichi@nitech.ac.jp. Fax: +81-52-735-7254. Tel: +81-52-735-7254.

Notes

The authors declare no competing financial interest.

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