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Organocatalytic Tail-to-Tail Dimerization of Olefin: Umpolung of Methyl Methacrylate Mediated by N-Heterocyclic Carbene

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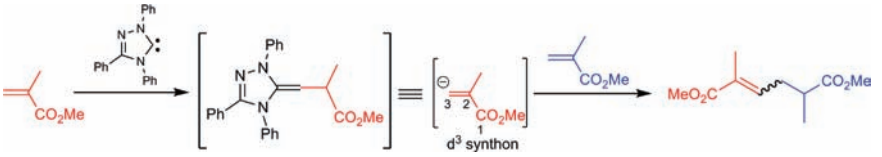
ABSTRACT



Highly selective tail-to-tail dimerization of methyl methacrylate has been realized by an *N*-heterocyclic carbene catalyst, giving dimethyl 2,5-dimethyl-2-hexenedioate with an *E*/*Z* ratio of 95:5 in 86% isolated yield. The umpolung mechanism is proposed on the basis of interception of the intermediates using ESI-MS analyses and deuterium-labeling experiments.

Tail-to-tail dimerization of functionalized olefins continues to be an important area of research because the resulting dimers are promising difunctional monomers for polycondensation. For this reason, significant efforts have been devoted to the dimerizations of methyl acrylate and acrylonitrile catalyzed by a variety of transition metal complexes such as Ru, Rh, Pd, and so on.[1−6] However, since there are potential difficulties in the selective C−C bond-forming event between electrophilic β-carbons, problems remain with substrate scope and reaction selectivity. In fact, there are only a few reports on the dimerization of

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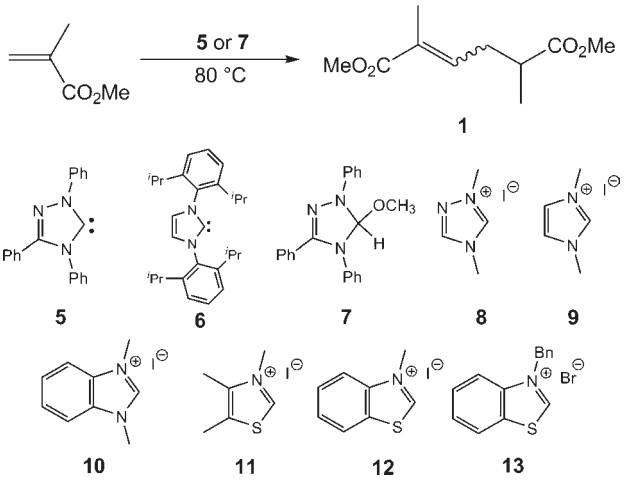
MMA[7,8] and none of other methacrylates, even though these are versatile synthetic routes to C8 olefins from C4 feedstocks. Specifically, the Oeheme and Tkatchenko groups reported the Pd-catalyzed dimerizations of MMA to give a mixture of the regioisomers, dimethyl 2,5-dimethyl-2-hexenedioate (**1**) and dimethyl 2-methylene-5-methylhexanedioate.[7] Recently, Hirano and co-workers reported an active Ru catalyst for the dimerization of MMA, however, accompanied with the formation of trimers.[8] Given that all of the tail-to-tail dimerizations of olefins reported to date are promoted by metal catalysts, we have focused on organocatalysis to improve the reaction selectivity and to expand the substrate scope.

N-Heterocyclic carbenes (NHCs) are versatile and highly nucleophilic organocatalysts, particularly for umpolung reactions of aldehydes.[9] However, much less attention has been directed to transformation of olefin. Previously, Enders et al. reported that the reactions of NHC with dimethyl fumarate or maleimides provide the 1:1 adducts through the conjugate addition and the subsequent proton transfer.[10] Ye et al. carried out the NHC-catalyzed aza-Morita–Baylis–Hillman reaction of cyclic enones.[11] Recently, Chen et al. performed the rapid polymerization of MMA and methylene butyrolactones by a frustrated Lewis pair of NHC and $Al(C_6F_6)_3$.[12] Interestingly, Fu et al. reported the NHC-catalyzed umpolung of Michael acceptors.[13] The *intramolecular* β-alkylation of α,β-unsaturated esters, amides, and nitriles was realized via the S_N2 reaction of the nucleophilic β-carbon with alkyl halide or tosylate groups.

Our initial interest in the nucleophilic reactivity of NHC toward electron-deficient olefins led us to explore the possibility of NHC-initiated zwitterionic polymerization[14] of MMA. However, contrary to our expectations, MMA was selectively converted to the tail-to-tail dimer, **1**, in the presence of catalytic amounts of NHC **5**. This unprecedented finding prompted us to undertake the present study. We herein report the highly selective tail-to-tail dimerization of methacrylates catalyzed by NHC. A reaction mechanism involving an *intermolecular* umpolung is proposed on the basis of interception of the intermediates using ESI-MS analyses and deuterium-labeling experiments.

Table 1. Optimization of Tail-to-Tail Dimerization of MMA Catalyzed by NHC



entry	catalyst[a]	temp, °C	time, h	solvent	yield, %[b]	*E*/*Z*[c]
1	**5**	40	24	bulk	16	95/5
2	**5**	60	24	bulk	41	96/4
3	**5**	80	1	bulk	32	93/7
4	**5**	80	8	bulk	86	95/5
5	**6**	80	8	bulk	0	
6	**7**	80	1	bulk	14	96/4
7	**7**	80	24	bulk	66	95/5
8	**8**/^{t}BuOK[d]	80	8	bulk	0	
9	**9**/^{t}BuOK[d]	80	8	bulk	tr[f]	
10	**10**/^{t}BuOK[d]	80	8	bulk	0	
11	**11**/^{t}BuOK[d]	80	8	bulk	0	
12	**12**/^{t}BuOK[d]	80	8	bulk	0	
13	**13**/^{t}BuOK[d]	80	8	bulk	0	
14	**5**	80	8	toluene[e]	85	95/5
15	**5**	80	8	DOX[e]	84	95/5
16	**5**	80	8	DME[e]	77	95/5
17	**5**	80	8	CH_3CN[e]	77	95/5
18	**5**	80	8	DCE[e]	43	95/5
19	**5**	80	8	DMF[e]	32	95/5
20	**5**	80	8	DMSO[e]	28	96/4

[a] Using 10 mol % of the NHCs (**5**, **6**) or the NHC precursors (**7**–**13**). [b] Isolated yield. [c] Calculated by ^{1}H NMR spectrum. [d] NHCs were generated in situ by the addition of 1.0 equiv of ^{t}BuOK relative to the NHC precursors. [e] [MMA] = 3.0 mol/L. [f] Detected by GC.

We first examined the catalytic activities of not only NHCs, either isolated (**5**, **6**) or generated in situ from the precursors (**7**–**13**), but also other organic nucleophiles such as PBu_3, PPh_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at 0–80 °C (Table 1 and full data in Supporting Information). Interestingly, the dimerization was catalyzed only by NHC **5** and its methanol adduct **7** (Table 1, entries 1–13). A catalyst system of **9**/^{t}BuOK gave a trace amount of **1** detected by GC analysis, and the other NHCs and the phosphine and amine nucleophiles showed no activity.

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Table 2. Tail-to-Tail Dimerization of Methacrylates Catalyzed by **5** at 80 °C

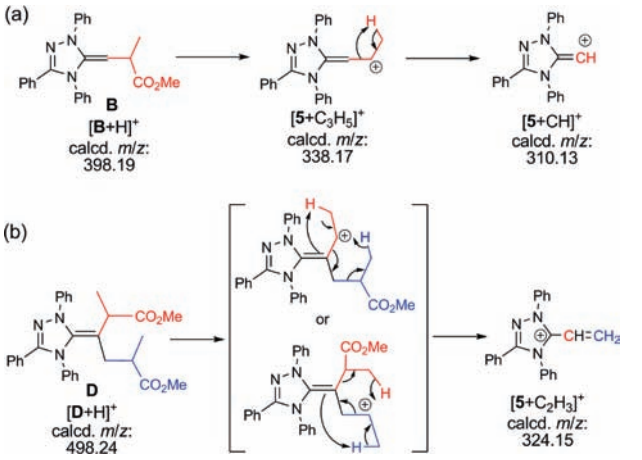
entry	substrate[a]	time, h	solvent	yield, %[b]	*E*/*Z*[c]
1	^{t}BMA	8	bulk	55	98/2
2	^{t}BMA	24	bulk	81	97/3
3	BnMA	8	bulk	81	88/12
4	DMAEMA	8	bulk	87	93/7
5	MMA-d_8	8	toluene[d]	80	98/2
6	MMA-d_2	8	toluene[d]	75	96/4

[a] ^{t}BMA, *tert*-butyl methacrylate; BnMA, benzyl methacrylate; DMAEMA, *N*,*N*-dimethylaminoethyl methacrylate; MMA-d_8, methyl methacrylate-d_8; MMA-d_2, methyl methacrylate-3,3-d_2. [b] Isolated yield. [c] Calculated by ^{1}H NMR (entries 1−4) or ^{2}H NMR (entries 5 and 6). [d] [MMA] = 3.0 mol/L.

Although the dimerization catalyzed by **5** was sluggish at 40 and 60 °C (entries 1 and 2), MMA was completely consumed at 80 °C within 8 h to afford **1** with an *E*/*Z* ratio of 95:5 in 86% isolated yield (entry 4). It is noteworthy that no other isomeric dimers and oligomers were produced except for a trace amount of a trimer.[15] Since a portion of MMA was recovered as the 1:1 and 1:2 adducts of **5** with MMA (see below), **1** was not quantitatively obtained. However, this organocatalytic procedure offers an efficient and practical advantage for the selective production of **1**. NHC precursor **7** is thermally converted to **5** at 80 °C by the loss of methanol.[10] Thus, the dimerization by **7** slowly proceeded via the in situ generation of **5**, giving **1** in 66% yield at 80 °C for 24 h (entries 6 and 7). Precursor **7** is air-stable, thereby making it convenient to handle. The dimerization catalyzed by **5** efficiently proceeded in a variety of solvents such as toluene, 1,2-dimethoxyethane (DME), 1,4-dioxane (DOX), and acetonitrile to give **1** in ∼80% yields (entries 14−17), whereas 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) lowered the yields (30−40%) (entries 18−20). The dimerizations of several substrates such as *tert*-butyl, benzyl, and *N*,*N*-dimethylaminoethyl methacrylates (^{t}BuMA, BnMA, and DMAEMA) were performed under the optimal condition (Table 2, entries 1−4). The corresponding dimers (**2**−**4**) were obtained in high yields, though the rate of the ^{t}BMA dimerization was relatively low.

To elucidate the reaction mechanism, we intercepted the intermediates by high-resolution ESI(+)-MS and tandem MS (MS/MS) experiments. The reaction mixture (Table 1, entry 14) was diluted with methanol and then infused into the ESI source. The mass spectrum revealed two intense peaks at *m*/*z* 398.19 and 498.24 (Figure S17, Supporting Information), which agree with the calculated *m*/*z* values for the protonated forms of the 1:1 and 1:2 adducts of **5** with MMA, respectively (**B**, **5** + MMA; **D**, **5** + 2MMA, Scheme 1). The ESI(+)-MS/MS spectrum of the [**B** + H]$^+$ peak showed an intense peak of *m*/*z* 310.14 and a small peak of *m*/*z* 338.17 corresponding to fragments of [**5** + CH]$^+$ and [**5** + C_3H_5]$^+$, respectively (Figure S18 in Supporting Information). Presumably, these fragments were formed by the consecutive loss of methoxycarbonyl group and ethylene from **B** as shown in Scheme 1(a). The ESI(+)-MS/MS spectrum of the [**D** + H]$^+$ peak showed a peak at *m*/*z* 324.15 corresponding to a fragment of [**5** + C_2H_3]$^+$ (Figure S19 in Supporting Information) This fragmentation would occur by the consecutive loss of methoxycarbonyl group, ethylene, and methyl acrylate (Scheme 1 (b)). These MS/MS analyses allow us to understand the structures of **B** and **D**.

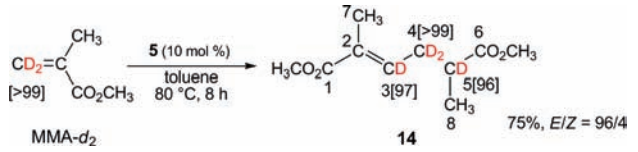
Scheme 1. Possible Fragmentations of Reaction Intermediates **B** (a) and **D** (b)



To obtain further evidence for the reaction mechanism, we performed the dimerizations of methyl methacrylate-d_8 (MMA-d_8) and methyl methacrylate-3,3-d_2 (MMA-d_2). The corresponding dimers were obtained in good yields (Table 2, entries 5 and 6, Scheme 2). Comparing the ^{1}H NMR spectrum of the dimer of MMA-d_2 (**14**) with that of **1**, the signals for methyl protons (CH_3CD) on C-8 became singlet, and those for the protons on C-3, -4, and -5 disappeared (Figures S1 and S9 in Supporting Information). Alternatively, the proton-decoupled ^{2}H NMR spectrum of **14** indicated the exclusive presence of the deuteriums on these three carbons by comparison with that of the MMA-d_8 dimer (**15**) (Figures S10 and S12 in Supporting Information). Additionally, the ^{13}C NMR spectrum of **14** showed the triplet and quintet signals due to the carbon-deuterium coupling at δ 31.4 (quin, C-4), 38.2 (t, C-5), and 138.2 (t, C-3) ppm (Figure S11 in Supporting Information). It is therefore clear that the dimerization of MMA-d_2 selectively provides dimer **14**, which is deuterated at C-3, -4, and -5 (Scheme 2). Thus, this dimerization involves the transfer of a deuterium of MMA-d_2 to the tertiary carbon (C-5) of **14**. Importantly, no scrambling between α-methyl protons and deuteriums takes place during the reaction. We therefore exclude the possibility of reaction mechanisms involving the scrambling, such as the hydrogen

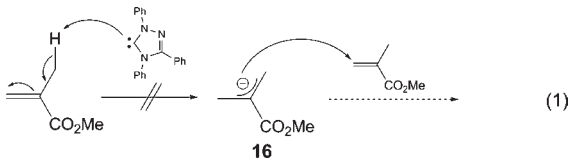
(15) A trimer was detected by ESI(+)-MS measurement in the crude mixture of the dimerization, though it was not observed by ^{1}H NMR (600 MHz) spectroscopy. See Figure S14, S15, S18, and S19 (Supporting Information).

Scheme 2. Tail-to-Tail Dimerization of MMA-d_2 (Entry 6 in Table *2*)[a]



[a] Values in brackets indicate the percentage of deuterium incorporation estimated from ^{1}H NMR.

abstraction and the subsequent conjugate addition of allyl anion **16** to MMA (eq 1).



From the above-mentioned results of the ESI-MS analyses and deuterium-labeling experiments, we propose the reaction mechanism shown in Figure 1. The nucleophilic attack of **5** to the β-carbon of MMA generates zwitterionic enolate **A**, followed by transfer of the methylene proton, which is activated by the adjacent carbocation. The resulting key intermediate **B** is a β-acylvinyl anion equivalent[16] (d^3 synthon). Importantly, the polarity of the β-carbon of MMA is reversed from electrophilic to nucleophilic during this process (a^3 to d^3 umpolung). The conjugate addition of **B** to another MMA molecule allows the tail-to-tail bond formation. The tertiary proton of the resulting enolate **C** is reactivated and transfers via a six-membered ring transition state to give intermediate **D**. The acidic proton of **D** transfers to the original carbon, generating enolate **E**. An intramolecular 1,2-proton shift of **D** is not probable, because the free energy barrier of such a three-membered ring transition state is very high.[17] Finally, the electron transfer of **E** produces **1**, regenerating NHC **5**. The proton transfers of **A** and **C** to form **B** and **D** would be much faster than their conjugate additions to MMA, thus allowing the dimerization to proceed selectively without forming trimers and oligomers.

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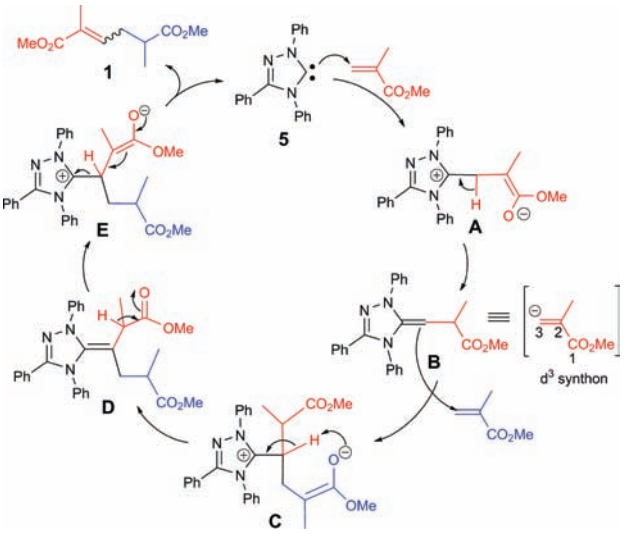

Figure 1. Proposed mechanism.

In conclusion, we have shown the highly selective tail-to-tail dimerization of methacrylates catalyzed by NHC. The ESI-MS analyses and the deuterium-labeling experiments indicated that umpolung of the β-carbon is responsible for the C−C bond formation. This is the first organocatalytic tail-to-tail dimerization of olefin and also the first NHC-catalyzed *intermolecular* umpolung reaction of a Michael acceptor. We expect that this procedure will provide a versatile platform for transformation of electron-deficient olefins to a range of valuable fine chemicals. Further research along these lines is in progress in our laboratory.

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Supporting Information Available. Selected experimental procedures, spectroscopic data, and full data of the dimerization experiments. This material is available free of charge via the Internet at http://pubs.acs.org.