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Organocatalytic head-to-tail dimerization of methacrolein via conjugate addition of methanol: an alcohol activation mechanism proved by electrospray ionization mass spectrometry

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ABSTRACT

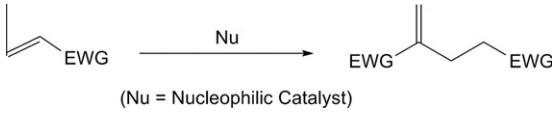
The head-to-tail dimerization of methacrolein via the conjugate addition of methanol is catalyzed by various organic bases, such as an amine, phosphine, and N-heterocyclic carbene, to give 2,4-dimethyl-2-methoxymethylpentane-1,5-dial in moderate yields. Based on the interpretation of the key intermediates by electrospray ionization mass spectrometry, we propose a reaction mechanism involving the initial conjugate addition of the organic bases to methacrolein to generate a zwitterionic base followed by the activation of methanol.

Introduction

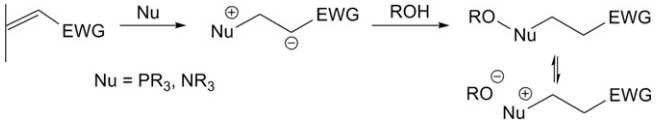
Head-to-tail dimers of functionalized olefins can be promising monomers for stepwise and chain polymerizations. Organic bases are effective catalysts for the dimerization of activated olefins such as methyl acrylate and acrylonitrile (Scheme 1).[1] However, the selective dimerization of other reactive substrates has been only slightly reported because of their potential polymerizability. Almost half a century ago, patents reported that the conjugate addition of methanol to methacrolein (MACR) in the presence of several bases, such as alkali metal hydroxides and ammonium hydroxides, produced the head-to-tail dimer, 2,4-dimethyl-2-methoxymethylpentane-1,5-dial (**1**).[2] To our surprise, no attention has yet been paid to this dimerization, though aliphatic dialdehydes, such as glutaraldehyde, are useful reagents.

The hydroalkoxylation of an olefin is an important O–C bond forming reaction. Toste and co-workers reported the trialkylphosphine-catalyzed reactions of enones,[3] and Connon and co-workers reported the amine-catalyzed reactions of acrylates.[4] They proposed that the conjugate addition of the organic bases to olefins generates a zwitterionic intermediate that subsequently undergoes the deprotonation of an alcohol (Scheme 2). Recently, Scheidt and co-workers reported that N-heterocyclic carbene (NHC) also serves as an efficient catalyst for the hydroalkoxylation of enones.[5] In contrast to the amine and phosphine-catalyzed reactions, they proposed a mechanism involving direct deprotonation of alcohol by NHC. Since these organic catalysts act as either a Lewis or a Brønsted base, the mechanistic aspect has not been systematically understood and continues to be an important issue that has to be addressed.

We now report the head-to-tail dimerization of MACR via the conjugate addition of methanol with the aid of amine, phosphine, and NHC catalysts (Scheme 3). A reaction mechanism is proposed on the basis of the interpretation of the reaction intermediates using electrospray ionization mass spectrometry (ESI-MS).



Scheme 1. Head-to-tail dimerization of activated olefins (Rauhut–Currier reaction).



Scheme 2. Alcohol activation mechanism for the phosphine and amine-catalyzed hydroalkoxylation.

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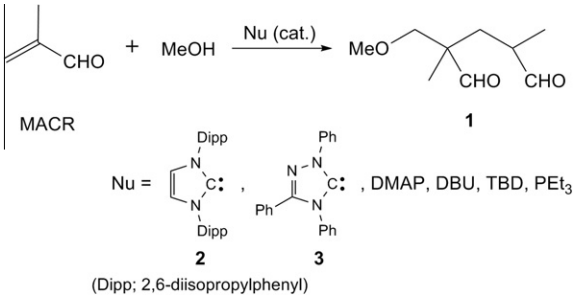


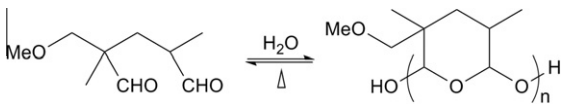
Scheme 3. Head-to-tail dimerization of MACR via conjugate addition of methanol catalyzed by organic bases (this work).

Results and discussion

The dimerization of MACR was examined using a variety of organic catalysts, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**2**), 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene (**3**), PEt_3, 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-(dimethylamino) pyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Two different concentrations of methanol were employed; [Alcohol]/[MACR] = 10 and 1. Methanol acted as both the solvent and reactant in the former case (entries 1–7), and THF was used as the solvent in the latter case (entries 8–15). The dimer **1** was obtained as a diastereomeric mixture (Figs. S1, S2, and S8, Supplementary data). Even with a low catalyst loading (0.70 mol %), moderate yields were observed in several entries. All the organic bases used, except for DABCO, could catalyze the dimerization, and the best yield was obtained using DBU and **2** (entries 6 and 8). When using **3**, DMAP, and DBU, an excess amount of methanol was required to promote the reaction. Even with the low concentration of methanol, the dimerization could be catalyzed by **2**, Et_3P, and TBD with comparable or higher yields (entries 8, 9, 11 and 15). The reaction with methanol-d_4 (entry 9) gave **1** with >99% and 78% deuterium incorporations at the methoxy group and tertiary C_4 position, respectively. Given that the NHCs catalyze a variety of umpolung reactions of aldehydes,[6] it is interesting to note that the aldehyde group of MACR remained unchanged during the present reaction.

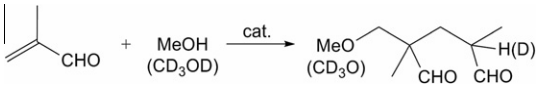
The distilled dimer **1** was stable for at least 3 days at 5 °C under nitrogen. However, the stirring of **1** in air for a few hours caused the viscosity to increase, and the resulting mixture gave broad ^1H NMR signals. The SEC profile showed that oligomerization occurred. The conversions of the aldehyde evaluated by ^1H NMR were 49% for 3 h and 81% for 27 h. Moisture in the air probably initiated the oligomerization by the nucleophilic reaction to the aldehyde carbon followed by intramolecular cyclization (Scheme 4). Interestingly, **1** could be recovered from the oligomer by distillation; heating it at 100 °C for 30 min under reduced pressure (2 mmHg) afforded **1** in an 88% yield, indicating an equilibrium between **1** and the oligomer. These characteristics are similar to those of glutaraldehyde.

Encouraged by the selective formation of **1**, we examined the various substrates listed in Table 2. The reactions were carried out for 16 h under the same conditions as entry 1 in Table 1. The corresponding dimers were not formed in all the entries, while hydromethoxylated products were obtained from methyl acrylate,



Scheme 4. Equilibrium between **1** and oligomer.

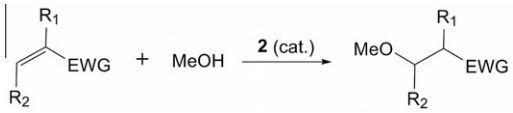
Table 1
Organocatalytic head-to-tail dimerization of MACR[a]

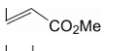
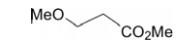
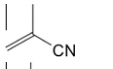
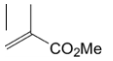
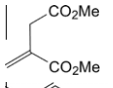
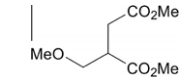
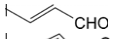
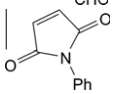
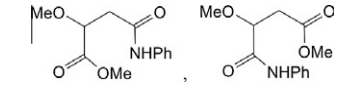


Entry	Cat. (0.70 mol %)	[Alcohol] /[MACR]	Alcohol	Yield (%)
1	**2**	10	MeOH	23
2	**3**	10	MeOH	28
3	PEt_3	10	MeOH	18
4	DABCO	10	MeOH	<1
5	DMAP	10	MeOH	11
6	DBU	10	MeOH	40
7	TBD	10	MeOH	24
8	**2**	1	MeOH	40
9	**2**	1	CD_3OD	32
10	**3**	1	MeOH	<1
11	PEt_3	1	MeOH	20
12	DABCO	1	MeOH	<1
13	DMAP	1	MeOH	<1
14	DBU	1	MeOH	<1
15	TBD	1	MeOH	30

[a] [MACR] = 2.0 mol/L, for 6 h, in THF (entries 8–15).

Table 2
Hydromethoxylation of activated olefins catalyzed by **2**[a]



Entry	Olefin	Product	Yield (%)
1			41
2		—	<1
3		—	<1
4			42
5		—	<1
6			>99

[a] For 16 h at rt, [**2**]/[olefin]/[MeOH] = 1:140:1400, [olefin] = 2.0 mol/L.

dimethyl itaconate, and *N*-phenyl maleimide. The ring-opened isomers were quantitatively produced from *N*-phenyl maleimide. The reactions of methacrylonitrile, methyl acrylate, and crotonaldehyde provide neither the hydromethoxylated product nor the dimers. Thus, MACR exhibits a unique reactivity for the selective dimerization.

Recently, high-resolution ESI(+)-MS and tandem MS (MS/MS) analyses have been used as powerful tools for investigating reaction mechanisms by the analysis of intermediates. For the reactions catalyzed by **1**, **2**, PEt_3, and DBU, the proton adducts of the key intermediates [Nu+2 MACR+MeOH] (Nu = **1**, **2**, PEt_3, and DBU) were detected by ESI(+)-MS (Fig. 1a and c, Figs. S3 and S6). The MS/MS experiment of these ions clearly gives fragment ions of $[Nu+2\ MACR+H]^+$ via the loss of methanol (Fig. 1b and d, Figs. S4 and S7). As shown in Figure 2, there are two possible structures for the intermediates, **4** and **5**. Their formation is dependent on the first step of the reaction cycle. **4** can be generated via the activation of methanol by an organic base, while **5** via the conjugate addition of the organic base to MACR. Considering fragmentation of the

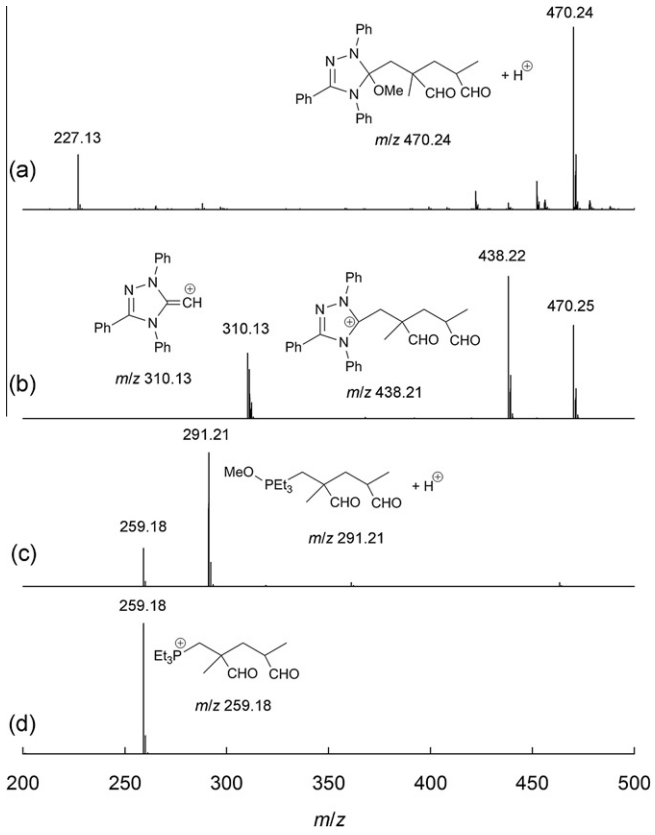


Figure 1. ESI(+)-MS spectra of the reaction solutions of entry 2 (a) and 3 (c) in Table 1. ESI(+)-MS/MS spectra of the ions of *m*/*z* 470.24 (b), and *m*/*z* 291.21 (d).

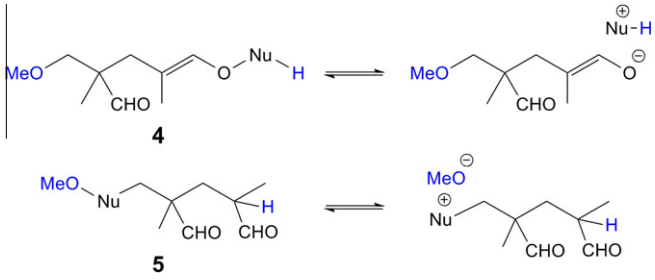
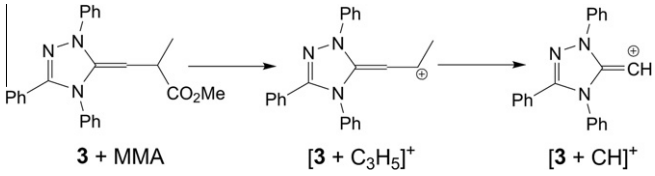


Figure 2. Two possible structures (**4**, **5**) of the intermediate.



Scheme 5. Fragmentation of the adduct of **3** and MMA (**3**+MMA).

proton adducts of **4** and **5** in the MS/MS spectra, [**4**+H]$^+$ would probably produce a fragment ion of [Nu+H]$^+$, while [**5**+H]$^+$ would readily lose methanol to give [Nu+2 MACR+H]$^+$. Therefore, it is reasonable to assume that **5** is the key intermediate. This conclusion is further supported by the fragment peak due to [**3**+CH]$^+$ in Figure 1b. This fragment is also observed in the MS/MS spectrum of the adduct of **3** and methyl methacrylate (**3**+MMA) (Scheme 5).[7] Therefore, the key intermediate of the present reaction should

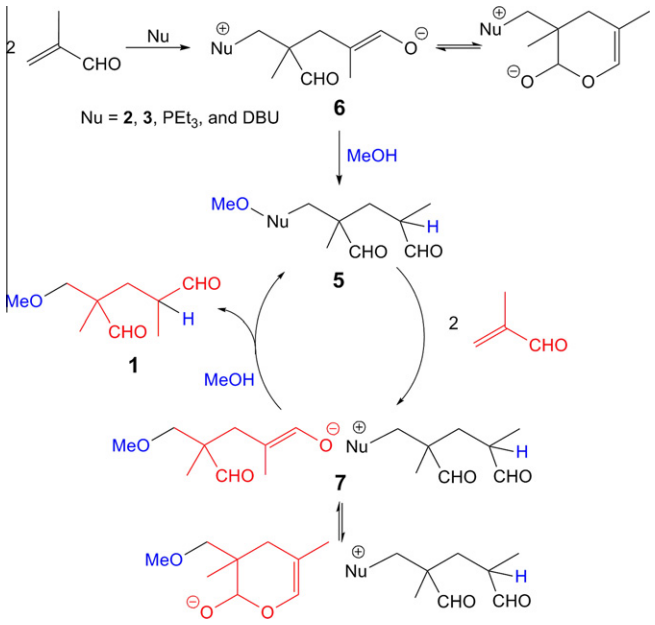


Figure 3. Proposed mechanism of the head-to-tail dimerization of MACR via the conjugate addition of methanol.

possess the C–C bond formed between the carbene carbon and the β-carbon of MACR.

Based on the analysis of the intermediates using ESI-MS, we propose the mechanism of the dimerizations catalyzed by **2**, **3**, Et_3P, and DBU in Figure 3. First, the consecutive conjugate addition of the organic base to two molecules of MACR generates the enolate **6**, which will be equilibrated with the hemiacetal alkoxide. The reaction of **6** with methanol gives **5**, and the conjugate addition of methoxide of **5** to two molecules of MACR results in the formation of **7**. Due to the equilibrium between **7** and the hemiacetal alkoxide, **7** was reluctant to undergo a further conjugate addition to MACR. The reaction of **7** with methanol produces the dimer, **1**, and regenerates **5**. This mechanism is similar to the previously reported phosphine and anime-catalyzed hydroalkoxylations.[3,4] It is known that NHCs serves as a Brønsted[8] and Lewis base.[7,8a,b,9] We propose that the direct activation of methanol by NHCs is unlikely in the present reaction. Additionally, NHC can promote the umpolung of methacrylates via the conjugate addition and the subsequent proton transfer,[7,9d] but this is not the case for MACR.

Conclusions

We have shown that the head-to-tail dimerization of MACR via the conjugate addition of methanol is catalyzed by organic bases, such as DBU, PEt_3, NHCs, producing an aliphatic dialdehyde. In addition, the NHC-catalyzed hydroalkylations of methyl acrylate, dimethyl itaconate, and *N*-phenyl maleimide are also reported. We succeeded in interpreting the key intermediates by ESI-MS, and thereby propose a catalytic cycle initiated by the conjugate addition of the organic bases to MACR to generate the zwitterionic intermediates, followed by the activation of methanol. We expect that such zwitterions generated in situ are versatile Brønsted bases for developing new organocatalysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.070.

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