ORGANIC
LETTERS

2013
Vol. 15, No. 23
5916–5919

N-Heterocyclic Carbene-Catalyzed Cyclotetramerization of Acrylates

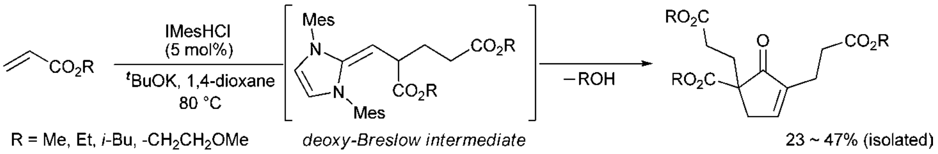
Shin-ichi Matsuoka,* Shoko Namera, Atsushi Washio, Koji Takagi, and Masato Suzuki

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

matsuoka.shinichi@nitech.ac.jp

Received August 2, 2013; Revised Manuscript Received November 1, 2013

ABSTRACT



N-Heterocyclic carbenes (NHCs) were found to catalyze the unprecedented cyclotetramerization of acrylates, producing the trisubstituted cyclopentenones in moderate yields. The proton or deuterium adducts of the deoxy-Breslow intermediate derived from NHC and two molecules of methyl acrylate were obtained. A reaction mechanism involving the new umpolung/cyclization sequence is proposed.

Catalytic oligomerizations of unsaturated compounds are important bond-forming reactions because they provide access to valuable chemicals such as higher olefins and cyclic products from simple chemical feedstocks. Among the activated olefins, methyl acrylate (MA) has been one of the most studied substrates due to its high reactivity toward nucleophiles or transition-metal complexes.[1] Indeed, the Rauhut–Currier reaction,[2] i.e., the head-to-tail dimerization, of MA is catalyzed by the trialkyl phosphines[3] or the metal complexes[4] to give the vinylidene dimer or trimer, which can be used as monomers for radical polymerizations.[5] Alternatively, the vinylene diester was obtained from MA by the tail-to-tail dimerization catalyzed by the transition metal complexes,[6] which can be an alternative synthetic pathway to adipinic acid. In addition, the catalytic trisannulation and cyclodimerization of acrylates to produce 1,3,5-benzenetricarboxylates[7] and a coumalate[8] have been reported. To the best of our knowledge, however, there are no other types of oligomerizations of MA or the catalytic tetramerization of activated olefins.[9]

N-Heterocyclic carbenes (NHCs) have been very useful catalysts for the umpolung reactions of aldehydes.[10] Recently, the reactions of NHCs with activated olefins have also gained attention.[11] The zwitterions generated from NHC with such olefins show an alternative reactivity: (1) proton transfer to generate enediamines, i.e., the deoxy-Breslow intermediates,[12−15] or (2) the further addition to

---

(1) For a review, see: Tembe, G. L.; Bandyopadhyay, A. R.; Ganeshpure, P. A.; Satish, S. *Catal. Rev.-Sci. Eng.* **1996**, *38*, 299.

(2) For a review, see: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069.

(3) For a selected example, see: (a) Trumbo, D. L.; Zander, R. A. *J. Polym. Sci., Polym. Chem.* **1991**, *29*, 1053. (b) Su, W.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 9499.

(4) For selected examples, see: (a) Yi., C. S.; Liu, N. *J. Organomet. Chem.* **1998**, *553*, 157. (b) Aresta, M.; Dibenedetto, A.; Quaranta, E. *Organometallics* **2000**, *19*, 4199. (c) Nakagawa, H.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2003**, 502.

(5) (a) Kobatake, S.; Yamada, B. *J. Polym. Sci., Polym. Chem.* **1996**, *34*, 95. (b) Hirano, T.; Yamada, B. *Polymer* **2003**, *44*, 347.

(6) For selected examples, see: (a) Pertici, P.; Ballantini, V.; Salvadori, P.; Bennett, M. A. *Organometallics* **1995**, *14*, 2565. (b) DiRenzo, G. M.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1996**, *118*, 6225. (c) Kaneko, Y.; Kanke, T.; Kiyooka, S.; Isobe, K. *Chem. Lett.* **1997**, 23. (d) Braunstein, P.; Chetcuti, M. J.; Welter, R. *Chem. Commun.* **2001**, 2508. (e) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6203. (f) Hirano, M.; Sakate, Y.; Komine, N.; Komiya, S.; Bennett, M. A. *Organometallics* **2009**, *28*, 4902.

(7) (a) Tamaso, K.; Hatamoto, Y.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2007**, *72*, 3603. (b) Jiang, H.-F.; Shen, Y.-X.; Wang, Z.-Y. *Tetrahedron Lett.* **2007**, *48*, 7542.

(8) Maeda, S.; Obora, Y.; Ishii, Y. *Eur. J. Org. Chem.* **2009**, 4067.

(9) Catalytic cyclotetramerization of 1,3-butadiene, an unactivated olefin: (a) Bosch, M.; Brookhart, M. S.; Ilg, K.; Werner, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2304. (b) Tobisch, S.; Werner, H. *Dalton Trans.* **2004**, 2963. (c) Bosch, M.; Werner, H. *Organometallics* **2010**, *29*, 5646.

(10) For selected recent reviews, see: (a) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (b) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (c) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786. (d) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (e) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.

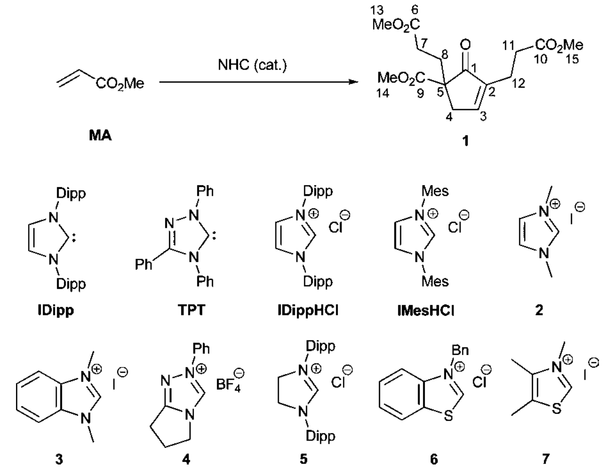
(11) For a review, see: Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906.

(12) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.

10.1021/ol4021942

electrophiles. In the former case, the further nucleophilic addition of the intermediates enables the umpolung reactions such as the cyclization,[12] tail-to-tail dimerization,[13] rearrangement,[14] and three-component reactions.[15] The latter also leads to the useful reactions such as the aza-Morita–Baylis–Hillman reaction,[16] cyclizations,[17] dimerization,[18] and polymerizations.[19] Although the NHC catalysis of activated olefins appears promising, the examined substrates are still limited to the disubstituted olefins, i.e., vinylenes and vinylidenes. We then turned our attention to highly reactive vinyl compounds as substrates and developed the selective cyclotetramerization of MA to form the trisubstituted cyclopentenone. We now report this unprecedented NHC catalysis and propose an umpolung/cyclization mechanism involving the deoxy-Breslow intermediate derived from the MA dimer.

Table 1. Catalyst Screening for the Cyclotetramerization of MA[a]



entry	cat.	base	solvent	temp (°C)	yield[b] (%)
1	IDipp		toluene	rt	0
2	IDipp		toluene	60	0
3	IDipp		THF	rt	trace
4	IDipp		THF	60	22
5	TPT		THF	60	0
6	TPT		bulk	80	0
7	IDippHCl	^{t}BuOK	THF	60	28
8	IMesHCl	^{t}BuOK	THF	60	35
9	**2**	^{t}BuOK or DBU	THF	60	0
10	**3**	^{t}BuOK or DBU	THF	60	0
11	**4**	^{t}BuOK or DBU	THF	60	0
12	**5**	^{t}BuOK or DBU	THF	60	0
13	**6**	^{t}BuOK or DBU	THF	60	0
14	**7**	^{t}BuOK or DBU	THF	60	0

[a] 10 mol % of catalyst, 10 mol % of base, for 24 h. [b] Isolated yield.

The reaction of MA was initially evaluated using 10 mol % of IDipp in THF at 60 °C for 24 h (entry 4 in Table 1). After the purification of the crude product by silica gel column chromatography, compound **1** was isolated as a pale yellow oil in 22% yield. The high-resolution ESI-MS indicated the sodium adduct ion at *m*/*z* 335.1094, suggesting the molecular formula of $C_{15}H_{20}O_7$. The IR spectrum showed absorption bands due to unconjugated ester carbonyls at 1732 cm^{-1} and the carbonyl of 2-cyclopentene-1-one at 1702 cm^{-1}. The ^1H NMR spectrum (Figure S1, Supporting Information) showed a singlet olefinic proton (δ 7.40, H-3), three methoxy protons (δ 3.66, 3.67, 3.69), and diastereotopic methylene doublets (δ 2.49, 3.11, H-4). The protons of two methylene groups (H-11, 12) were observed as a singlet at the same chemical shift (δ 2.54), which was confirmed by an HMQC experiment (Figure S6). In the COSY spectrum (Figure S4, Supporting Information), the olefinic proton (H-3) and the methylene protons (H-7) were coupled to the diastereotopic protons (H-4) and the methylene protons (H-8), respectively. The ^{13}C NMR spectrum (Figure S4, Supporting Information) indicated the presence of a ketone carbonyl carbon (δ 204.37, C-1), tertiary and quaternary olefinic carbons (δ 157.18, C-3; δ 142.67, C-2), and a quaternary aliphatic carbon (δ 57.30, C-5). The 2D INADEQUATE (Figure S7, Supporting Information) displayed 12 $^{13}C-^{13}C$ correlations; thus, all signals in the ^{13}C NMR spectrum were assigned. In addition, the HMBC spectrum (Figures S8–S10, Supporting Information) showed 12 ^2J and 18 ^3J reasonable correlations. Collectively, these experiments proved the chemical structure of **1**.

The catalyst screening and optimization were then performed (Tables 1 and 2). The reaction with 10 mol % of IDipp in THF or toluene at rt or 60 °C suggested that high temperatures and polar solvents are required (entries 1–4 in Table 1). This reaction also proceeded with the NHC precursors IDippHCl or IMesHCl and ^{t}BuOK; however, IMesHCl showed the better activity (entries 7 and 8 in Table 1). TPT and the NHC precursors **2-7** with ^{t}BuOK or DBU did not produce **1** (entries 5, 6 and 9–14 in Table 1). The optimization was performed using 5 mol % of IMesHCl for 24 h (Table 2). When the reactions were carried out in THF at 60 °C using ^{t}BuOK, K_2CO_3, Cs_2CO_3, and DBU as bases, the best yield was obtained with ^{t}BuOK (entries 1–4 in Table 2). Among THF, CH_2Cl_2, 1,2-dimethoxyethane, and 1,4-dioxane at 40–80 °C using ^{t}BuOK, the best isolated yield (47%) was obtained in 1,4-dioxane at 80 °C (entries 1 and 5–7 in Table 2). The conversion and ^1H NMR yield were 92 and 60%, respectively (entry 7). Under these optimized conditions, the yield was moderate (49%) even at a 10 mol % catalyst loading

---

(13) (a) Matsuoka, S.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722. (b) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412. (c) Kato, T.; Ota, Y.; Matsuoka, S.; Takagi, K.; Suzuki, M. *J. Org. Chem.* **2013**, *78*, 8739.

(14) (a) Atienza, R. L.; Roth, H. S.; Scheidt, K. A. *Chem. Sci.* **2011**, *2*, 1772. (b) Atienza, R. L.; Scheidt, K. A. *Aust. J. Chem.* **2011**, *64*, 1158.

(15) Matsuoka, S.; Tochigi, Y.; Takagi, K.; Suzuki, M. *Tetrahedron* **2012**, *68*, 9836.

(16) (a) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (b) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825.

(17) (a) Raveendran, A. E.; Paul, R. R.; Suresh, E.; Nair, V. *Org. Biomol. Chem.* **2010**, *8*, 901. (b) Chen, X.-Y.; Sun, L.-H.; Ye, S. *Chem.—Eur. J.* **2013**, *19*, 4441.

(18) Matsuoka, S.; Shimakawa, S.; Takagi, K.; Suzuki, M. *Tetrahedron Lett.* **2011**, *52*, 6835.

(19) (a) Zhang, Y.; Miyake, G. M.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2010**, *49*, 10158. (b) Zhang, Y.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2012**, *51*, 2465.

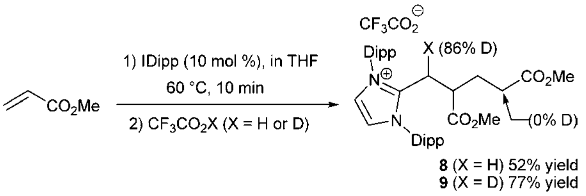
Table 2. Cyclotetramerization of Acrylates Catalyzed by IMes[a]

entry	substrate[b]	[IMesHCl] (mol %)	base	solvent[c]	temp (°C)	yield[d] (%)
1	MA	5	^{t}BuOK	THF	60	30
2	MA	5	K_2CO_3	THF	60	9
3	MA	5	Cs_2CO_3	THF	60	9
4	MA	5	DBU	THF	60	5
5	MA	5	^{t}BuOK	CH_2Cl_2	40	trace
6	MA	5	^{t}BuOK	DME	80	34
7	MA	5	^{t}BuOK	DOX	80	47 (60)[e]
8	MA	10	^{t}BuOK	DOX	80	49
9	MA	2	^{t}BuOK	DOX	80	24
10	EA	5	^{t}BuOK	DOX	80	37
11	*i*-BA	5	^{t}BuOK	DOX	80	23
12	MEA	5	^{t}BuOK	DOX	80	31

[a] For 24 h. [b] EA = ethyl acrylate, *i*-BA = isobutyl acrylate, MEA = 2-methoxyethyl acrylate. [c] DME = 1,2-dimethoxyethane, DOX = 1,4-dioxane. [d] Isolated. [e] The value in parentheses indicates ^{1}H NMR yield.

and decreased to 24% at 2 mol % (entries 8 and 9 in Table 2). No dimers, trimers, and other tetramers were observed in the GC analysis of the crude product. A portion of MA was recovered as 1:2, 1:3 and 1:4 adducts of NHC and MA, which were detected by ESI-MS (Figure S20, Supporting Information). Under the optimal conditions (entry 7 in Table 2), the cyclotetramerizations of ethyl, isobutyl, and 2-methoxyethyl acrylates produced the corresponding cyclic tetramers in 37, 23, and 31% isolated yields, respectively (entries 10–12 in Table 2).

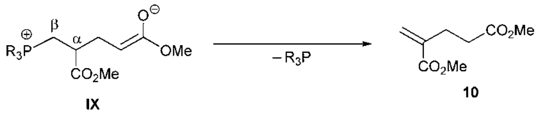
Scheme 1. Reaction of MA with IDipp Quenched by CF_3CO_2X (X = H or D)



The reaction mechanism was next considered. The reaction for 10 min under the conditions of entry 4 in Table 1, followed by the addition of CF_3CO_2H, produced compound **8**[20] in 52% yield (Scheme 1) which was estimated by ^{1}H NMR spectroscopy. The use of CF_3CO_2D instead resulted in the formation of **9** with the selective deuterium incorporation at the β carbon not the α carbon of the terminal ester. These results indicated that this catalysis involves the intermediate II (see Figure 1) derived from the NHC and two molecules of MA. This also means the nucleophilic reaction of II with the third MMA being slow.

We thus propose two possible reaction mechanisms in Figure 1. The Michael addition of NHC with two molecules of MA generates the zwitterionic ester enolate **I**. The proton transfer then results in the formation of the key deoxy-Breslow intermediate, **II**, in which the NHCs turn the β-carbon of MA nucleophilic. The head-to-tail dimer **10** was not detected by GC analysis during the catalysis, indicating that the α proton of **I** was not transferred. The umpolung and the subsequent Michael addition allow the bond formation between the β-carbons of MA. This Michael addition (**II**→**VI**) is relatively slow in comparison with the consecutive conjugate addition (NHC→**I**) and the proton transfer (**I**→**II**) processes, as suggested by the results shown in Scheme 1. In the proposed cycle A, **II** reacts with two molecules of MA to generate the enolate **III**. The proton transfer of **III** generates **IV**, which then undergoes cyclization to form **V**. The deprotonation by the methoxide ion produces **1** and regenerates the NHC. In the proposed cycle B, the reaction of **II** with MA to generate **VI** is followed by the cyclization and the subsequent elimination of NHC to give **VIII**. The NHC-catalyzed Michael addition of **VIII** to MA produced **1**.[21] When the reaction mixture, produced under the conditions of entry 8 in Table 1 for 1 h, was subjected to ESI-MS spectrometry, we observed five intense signals corresponding to $[\mathbf{1} + \mathrm{Na}]^+$, $[\mathrm{IMes} + 2\mathrm{MA} + \mathrm{H}]^+$, $[\mathrm{IMes} + 3\mathrm{MA} + \mathrm{H}]^+$, $[\mathrm{IMes} + 4\mathrm{MA} - \mathrm{MeO}]^+$, and $[\mathrm{IMes} + 4\mathrm{MA} + \mathrm{H}]^+$ (Figure S20, Supporting Information). The latter two ions correspond to **V** and **IV** in cycle A. In contrast, for the intermediates in cycle B, the sodium or proton adduct ions of **VIII** were not observed, and $[\mathrm{IMes} + 3\mathrm{MA} - \mathrm{MeO}]^+$ corresponding to **VII** was detected but with a low intensity. Thus, we postulated that cycle A is preferred.

NHC has a nucleophilic reactivity similar to trialkyl phosphines but promotes the distinct catalysis for MA. Trialkyl phosphine catalyzes the Rauhut-Currier reaction of MA to give the dimer **10** through the transfer of the α- proton of the zwitterionic ester enolate intermediate (**IX**) (eq 1).[2,3] The transfer of the β-proton of **IX** to form the phosphorus ylide is unfavorable. In contrast, NHC is ineffective for the Rauhut-Currier reaction of MA. Since the deoxy-Breslow intermediates are relatively stable as previously pointed out,[22] the transfer of the β-proton of **I** is predominant over the α-proton.

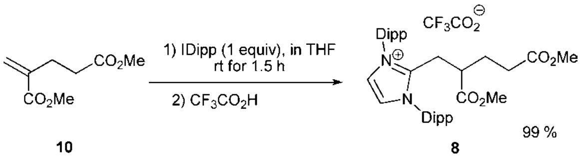


(eq 1)

It is also noteworthy that the structure of NHC has significant effects on the catalysis of activated olefins.

---

[20] Compound **8** was alternatively synthesized from the reaction of IDipp with the MA dimer **10** in 99% yield.



[21] The NHC-catalyzed Michael additions of 1,3-dicarbonyl compounds were reported; see: (a) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2009**, *351*, 1744. (b) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2011**, *17*, 2266.

[22] Zhao, L.; Chen, X. Y.; Ye, S.; Wang, Z. X. *J. Org. Chem.* **2011**, *76*, 2733.

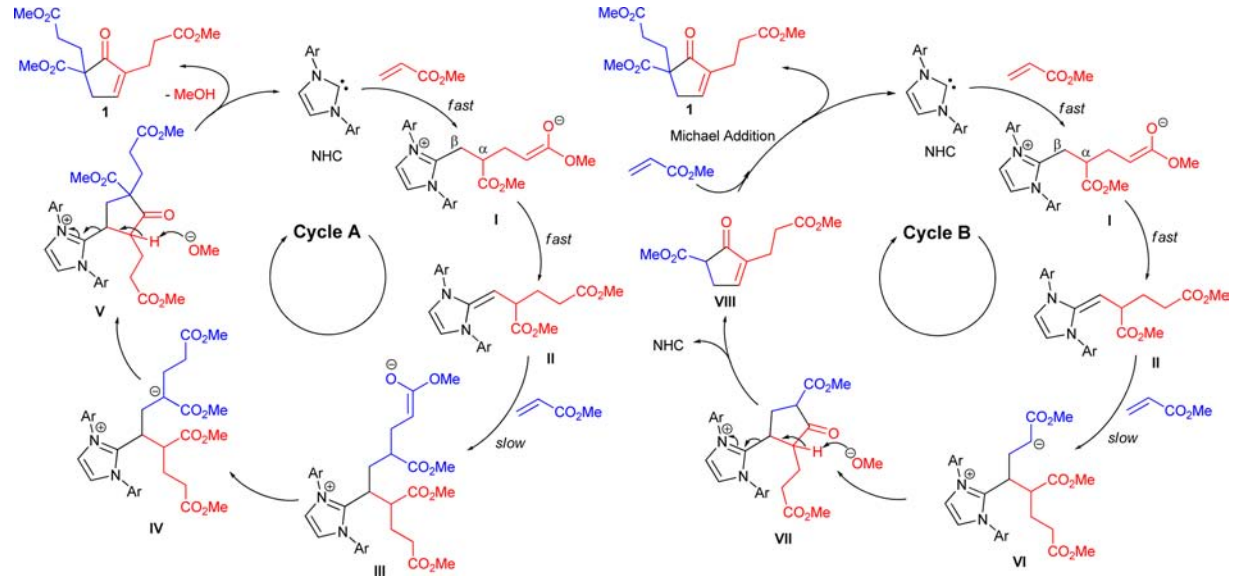
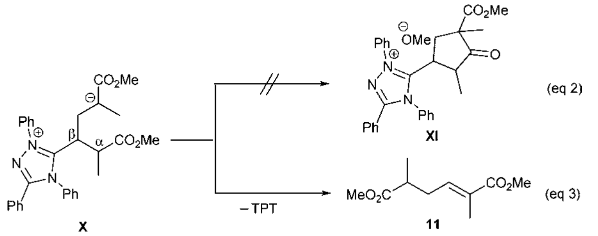


Figure 1. Possible reaction mechanisms. Cycle A is preferred.

Indeed, IMes catalyzes the cyclotetramerization of MA and produces the stable single adduct with methyl methacrylate.[19b] In contrast, TPT catalyzes the tail-to-tail dimerizations of methacrylates through the enolate intermediate **X** (eqs 2 and 3).[13] Although this enolate is an analogue of **IV** and **VI**, it does not undergo cyclization to generate **XI** (eq 2) but instead the proton transfer with the elimination of TPT to produce **11** (eq 3). One reason for this difference may be that the α-proton of **X** shows a higher acidity than those of **IV** and **VI** due to the relatively stronger electron-withdrawing ability of the triazolium ring. This interesting difference between these two major NHC catalysts suggests that the design of the NHC structure is important for future reaction discovery.



In conclusion, we have determined that the cyclotetramerization of acrylates catalyzed by IMes produces the trisubstituted cyclopentenones. The key deoxy-Breslow intermediate was obtained as the proton or deuterium adducts, and the other intermediates were detected by ESI-MS, leading us to propose the reaction mechanism. This NHC catalysis is remarkable since (1) this is the first cyclotetramerization of an activated olefin and (2) the first reaction of NHC with a vinyl compound, which involves (3) the first example of the Breslow type intermediate derived from two electrophiles and (4) is the first catalytic cascade of the umpolung of Michael acceptors followed by cyclization. Further work is now in progress to expand the scope of this cascade.

Acknowledgment. We thank Professor Akihiro Yoshino and Masato Taki at Nagoya Institute of Technology for the measurement of 2D INADEQUATE. This work was partially supported by a Grant-in-Aid for Scientific Research for Young Scientists (B) No. 24750102.

Supporting Information Available. Experimental section; ^{1}H, ^{13}C, and 2D NMR and ESI-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.