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Autocatalytic Domino Michael Reaction Leading to Bicyclo[2.2.2]octane-2,5-dione Derivatives

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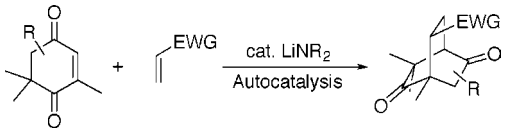
ABSTRACT



In the presence of a catalytic amount of lithium amide, the reaction of oxophorone with electron-deficient olefins afforded bicyclo[2.2.2]-octane-2,5-dione derivatives in high yields. The reaction proceeds autocatalytically by an enolate of bicyclo[2.2.2]octane-2,5-dione, generated by an initial domino Michael reaction.

The importance of the domino reaction,[1] a consecutive bond-forming reaction as a result of previous reaction, is now increasing in view of efficiency in organic syntheses. In the reaction, a multi-fold bond-forming reaction is realized in a one-pot operation enabling construction of more complex molecules that so far have been synthesized via multipot operations. Among many possibilities for designing domino reactions employing various fundamental synthetic transformations, nucleophilic domino reactions have played key roles especially for natural product syntheses. One of the well precedented nucleophilic domino reactions is the double Michael reaction of the kinetic enolate of cyclohexenone **1** with acrylate **4** leading to *endo*-bicyclo[2.2.2]octane derivatives **2** (Scheme 1).[2] The reaction required a stoichiometric amount of amide base **3** in aprotic media at low temperature to drive the domino reaction forward to the bicyclic compound **2** without equilibrating back to the substrates **1** and **4**. The amount of the base and the reaction conditions were critical.

Scheme 1

This domino reaction proceeds under mild reaction conditions with high regio- and stereoselectivity. Its generality and usefulness have been exemplified by its wide application[3] as a surrogate of a Diels−Alder reaction, which is not always suitable for construction of multiply functionalized bicyclo-[2.2.2]octane derivatives **2** in terms of yields and selectivity.[4]

As a part of our ongoing program directed toward development of the nucleophilic domino Michael reaction

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(1) Tietz, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 131. Posner, G. H. *Chem. Rev* **1986**, *86*, 831.
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(3) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem*. **2003**, *68*, 6096 and earlier references therein.
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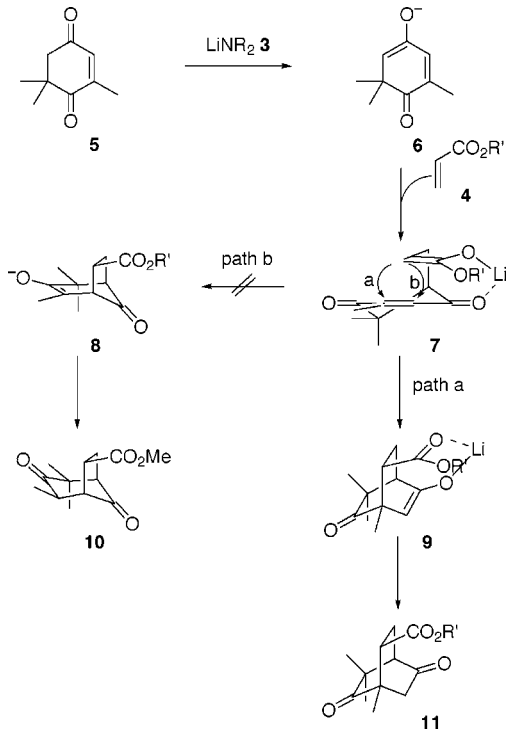
and its application to natural product syntheses,[5] we delineate herein for the first time a catalytic process based on oxophorone **5** and its congeners leading to bicyclo[2.2.2]-octane-2,5-dione derivatives **11**. If the intrinsically reversible nature of the Michael reaction is considered, the idea of a catalytic domino Michael reaction employing a catalytic amount of base is not unpredictable. However, there have been no precedents so far due to the kinetically controlled nature of the domino Michael reaction employing strong amide base **3** in aprotic media.

Construction of bicyclo[2.2.2]octane-2,5-dione derivatives was already reported by the domino Michael reaction of the kinetic enolate of cyclohexenone with 1-cycanoenamine and subsequent hydrolysis,[6] and we reported a more direct protocol by the domino Michael reaction of oxophorone **5** and its derivatives.[7] In the reaction, it was initially anticipated that the second Michael reaction would proceed kinetically via path b to afford bicyclo[3.2.1]octane derivative **10** due to steric as well as electronic reasons. However, we found that bicyclo[2.2.2]octane derivative **11** was stereoselectively obtained via path a as depicted in Scheme 2. The reason for

Scheme 2



the preferential formation of **11** is ambiguous but might be explained by intervention of the chelation-stabilized structure of intermediate enolate **7**, which might kinetically facilitate 6-*exo*-trig cyclization leading to **9**. The yields of this reaction, however, were not satisfactory. The utility of compound **11** (R = Me) has already been illustrated as a starting material of our recently reported total synthesis of valerianananoid A.[5b]

To improve the yields, the domino Michael reaction was re-examined changing combinations of acrylates, bases, or addend. Some representative results are compiled in Table 1.

Table 1. Catalytic Domino Michael Reaction of Oxophorone **5**[a]

entry	base **3** (R =)	amount of base (equiv)	acrylate **4** (R′ =)	product **11** yield (%)[b]
1[c]	benzyl	0.8	cyclohexyl	83
2		0.2		90
3		0.1		90
4	*i*-Pr	0.1		92
5	benzyl	0.1	methyl	90
6	*i*-Pr	0.1		81
7		1.0		29
8		0.1	2-naphthyl	75

[a] Reaction was carried out at −50 °C to room temperature in the presence of HMPA (4 equiv with respect to base). [b] Yield is based on oxophorone **5**. [c] HMPA was not added.

In entry 1, using 0.8 equiv of lithium bisbenzylamide and 1.2 equiv of cyclohexyl acrylate **4** (R′ = C_6H_{11}), the bicyclo-[2.2.2]octane-2,5-dione derivative **11** was obtained in 83% yield. Inspired by this result, the amount of base was successfully diminished to 0.2 equiv to give **11** in 90% yield as shown in entry 2, which was diminished again to 0.1 equiv (entry 3). The reaction was independent of amide base or the alkoxy moiety on acrylate **4**. Use of 0.1 equiv of base was sufficient (entries 3−6 and 8), while use of a stoichiometric amount of base decreased the yield (entry 7) probably due to the decomposition of the acrylate **4** (R′ = Me).

According to the reaction conditions in entry 4,[8] Table 1, the reaction of oxophorone **5** with other domino partners was investigated, and the results are listed in Table 2, entries 1−5. Acrylonitrile was a very reactive domino Michael partner (entry 1), affording bicyclic product **12** quantitatively in a shorter period of time (∼3 h) at lower temperature. In the reaction with vinyl phenyl sulfone, the domino Michael product **13** was accompanied with the bis-adduct **23** in 15% yield. Though the reaction of methyl methacrylate was sluggish, addition of an excess amount of HMPA improved

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(8) **Representative Procedure for Catalytic Domino Michael Reaction.** To a stirred solution of diisopropylamine (7 μL, 0.043 mmol) in THF (0.5 mL) was added *n*-butyllithium (28 μL, 1.56 M in *n*-hexane, 0.043 mmol) at 0 °C under a nitrogen atmosphere. Subsequently, a solution of oxophorone **5** (65 μL, 0.43 mmol) in THF (1.5 mL) and then HMPA (30 μL, 0.17 mmol) were added at −50 °C. After the mixture was stirred for 20 min, cyclohexyl acrylate (80 μL, 0.51 mmol) was added dropwise, and the resulting solution was stirred for 7 h with gradual warming to room temperature. The reaction was quenched by addition of dilute aqueous HCl, and the product was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. After evaporation of the solvent followed by medium-pressure LC (eluent = 1:3 ethyl acetate/*n*-hexane) afforded bicyclic compound **11**[7] (R′ = C_6H_{11}) (120 mg, 92%).

Table 2. Catalytic Domino Michael Reaction of Various Substrates

Entry	Enone	Yield (%)[b]
1	**5**	**12** (R = CN) 99
2	**5**	**13** (R = SO_2Ph) 36[c]
3[d]	**5**	**14** 89
4[d]	**5**	**15** 84
5[d]	**5**	**16** 64[e]
6	**17** (R = Me)	**18** 76
7	**19** (R = CH_2Ph)	**20** 73
8	**21** (R = allyl)	**22** 76

23

[a] All reactions were carried out with LDA (0.1 equiv) in the presence of HMPA (0.4 equiv) at −50 °C to room temperature for 8−20 h. [b] Yield is based on ene-dione. [c] Compound **13** was accompanied by the bis-adduct **23** in 15% yield. [d] Reaction was carried out in the presence of an equivalent amount of HMPA. [e] Compound **16** was accompanied by the stereoisomer **15** in 20% yield.

the yield in satisfactory level (entry 3). With dimethyl maleate as a Michael partner, the *trans*-diester **15** was afforded as a single diastereomer (entry 4). This result clearly indicates that the reaction proceeded via successive Michael pathways. Steric repulsion of the *syn*-diester gave rise to inversion of the carbanion center after the initial Michael reaction to provide *trans*-diester **15**. Dimethyl fumarate provided alternative *trans*-diester **16** as a major product (entry 5) whose formation was understood by approach of dimethyl fumarate from the less sterically hindered side in the initial Michael reaction at the expense of chelation-stabilized structures similar to the enolates **7** and **9**. However, a consistent reaction pathway for the stereospecific formation of **15** as well as **16** has yet to be reported.

In the reactions of substituted oxophorones **17**, **19**, and **21** with cyclohexyl acrylate **4**, bicyclic products **18**, **20**, and **22** were obtained in satisfactory yields (entries 6−8).

Stereochemistries of compounds **12**, **13**, **18**, **20**, **22**, and **24** were determined by W-type long-range coupling of the protons on carbons bearing electron-withdrawing groups as depicted in Figure 1, since determinations by the coupling

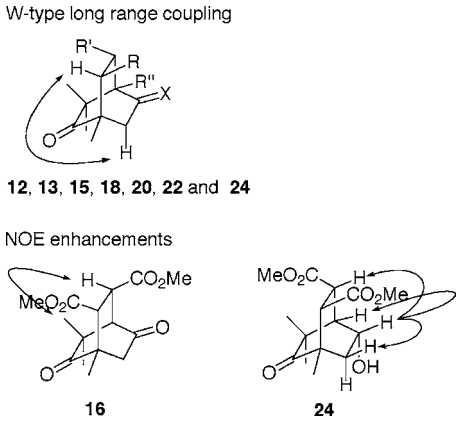
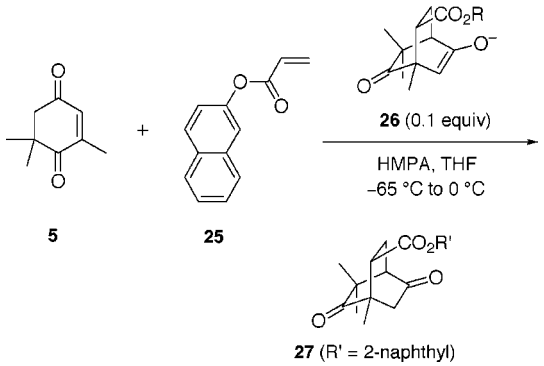


Figure 1.

constants were not reliable due to their close values. The stereochemistry of **16** was determined by NOE enhancement along with the absence of W-type coupling. Compound **15** was reduced by sodium borohydride to give alcohol **24** whose stereochemistry was established by NOE analysis along with W-type coupling.

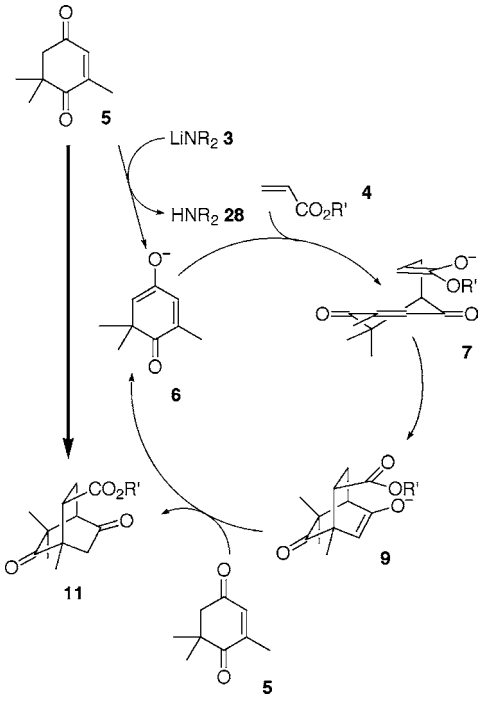
The result that supports the proposed reaction pathway was obtained by the following experiment. Enolate **26** (R = 8-phenylmenthyl) was generated from the corresponding bicyclic substrate and 0.5 equiv of LDA. Employing a catalytic amount of this enolate **26** (0.1 equiv) led to the reaction of oxophorone **5** with naphthyl acrylate **25**, affording bicyclic compound **27** in 81% yield based on the acrylate **25** (Scheme 3).

Scheme 3



Based on this finding, the following autocatalytic pathway is proposed as shown in Scheme 4. Regeneration of amide base **3** by the proton transfer to the enolate **9** from the secondary amine **28** is not possible, because the protons α

Scheme 4



to carbonyl group of bicyclo[2.2.2]octane-1-one (pK_a 28.1) are more acidic than diisopropylamine (pK_a 36).[9] Thus, it is apparent that the amide base **3** was not recycling as a catalyst. However, since the α-protons of cyclohexenone are estimated to be slightly more or comparably acidic to that of cyclohexanone (pK_a 26),[9] proton transfer from oxophorone **5** to the enolate **9** is possible. Thus, it is reasonable to justify that the bicyclic enolate **9** generated by the domino Michael reaction works autocatalyticaly as a base to oxophorone **5**. Amide base **3** plays a role as an initiator to generate oxophorone enolate **6**.

In summary, we have demonstrated for the first time a catalytic domino Michael reaction for construction of bicyclo[2.2.2]octane-2,5-dione derivatives **11**. It is worthy of note that the reaction proceeds autocatalytically. Further investigation is now in progress.

Supporting Information Available: Copies of NMR spectra of compounds **12**−**16**, **18**, **20**, **22**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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