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Sustainable domino Michael reaction catalyzed by a Brønsted base on silica gel: synthesis of bicyclo[2.2.2]octane-2,5-dione derivatives

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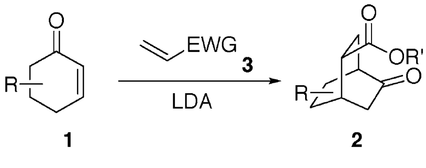
Abstract—Domino Michael reactions of oxophorone and its derivatives **4** with Michael partners **3** have been effected to give bicyclo[2.2.2]octane-2,5-dione derivatives **7** by a catalytic amount of a Brønsted base (NMAP-Li) generated from *N*-methylaminopropylated silica gel (NMAP) and *n*-BuLi. The NMAP pellets were efficiently reused up to six times in 86% average yield.

The domino reaction is a consecutive bond-forming reaction in one-pot operation by a reactive intermediate generated from a previous reaction. The reaction has attracted current interest of synthetic organic chemists due to its operational simplicity and economically as well as environmentally friendly nature. One of the fundamental nucleophilic domino reactions[1] is the double Michael reaction of a kinetic enolate of cyclohexenone **1** with an acrylate **3** (EWG = CO_2R') leading to stereoselectively *endo*-bicyclo[2.2.2]octane derivative **2** (Scheme 1),[2] which requires a stoichiometric amount of lithium diisopropylamide (LDA) in aprotic media to generate quantitatively a kinetic enolate of cyclohexenone **1**. The amount of the base was critical to drive the domino reaction forward to the bicyclic compound **2** without equilibrating back to the substrate **1** or a single Michael product.



Scheme 1. Domino Michael reaction of α,β-enone.

Usefulness of the domino Michael reaction has been demonstrated by its application to synthetic studies of several natural products.[3,4] One issue of the reaction, especially for large-scale preparation, was the use of an equivalent amount of an amide base. As a part of our efforts to respond to this issue, we previously reported for the first time a catalytic domino Michael reaction of oxophorone derivative **4**, in which 0.1 equiv of LDA was sufficient to provide the bicyclo[2.2.2]-octane-2,5-dione derivative **7** (Scheme 2).[5] The reaction proceeded via an autocatalytic pathway, in which bicyclic enolate **6** generated by the second Michael addition worked autocatalytically as the base to oxophorone **4**. The amide base plays the role of initiator to generate kinetic enolate **5** of oxophorone derivative **4**.

Our further interest in the reaction focused on recycled use of the base from environmental as well as economical points of view. Though a heterogeneous catalyst is more advantageous due to its easy recovery, there have been few heterogeneous bases that can generate a kinetic enolate of enone. We have reported that aminopropylated silica gel was a useful catalyst for 1,4-conjugate addition[6] and self-aldol condensation of unmodified aldehydes in ionic liquid[7] or supercritical carbon dioxide,[8] transesterification of β-ketoesters[9] or Knoevenagel

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Keywords: Domino reaction; Michael reaction; Silica gel anion; Heterogeneous base.

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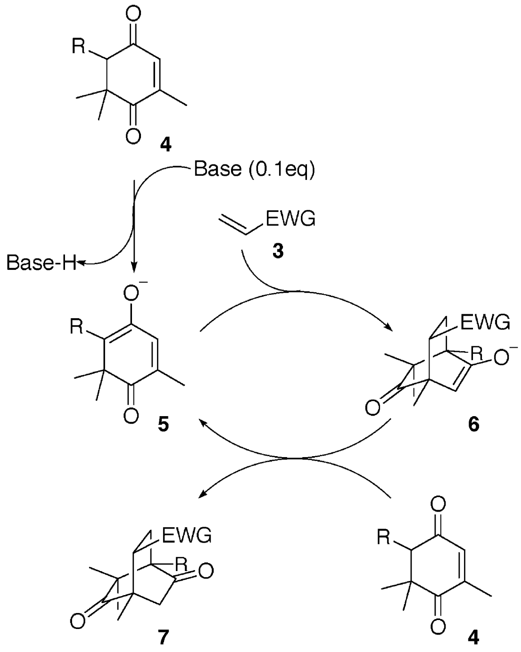
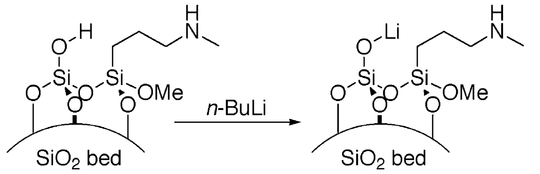


Scheme 2. Autocatalytic domino Michael reaction.

condensation in water,[10] which exemplified the utility of an organocatalyst grafted on silica gel due to its easy availability and wide applicability to a range of solvents in addition to mechanical and chemical stability with a wide surface area.

In this letter, we investigated the utility of the conjugate base of silica gel as a new heterogeneous Brönsted base catalyst, and disclose herein a sustainable catalytic domino Michael reaction of oxophorone and its derivatives **4** initiated by the base generated from *N*-methylaminopropylated silica gel (NMAP) and *n*-BuLi, leading to bicyclo[2.2.2]octane-2,5-dione derivatives **7** (Scheme 2).

NMAP was prepared according to the procedure cited in Ref. 7a. Since the amount of *N*-methylaminopropylated residue was 0.7 mmol/g by a combustion analysis and the amount of SiOH on the original silica gel was 2.8 mmol/g, the amount of ungrafted SiOH residue was roughly estimated to be 1.4 mmol/g, which means almost a half of the silanols was grafted. Since acidity of silanols was estimated to be pK_a 4.5,[11] it is reasonable to justify that the silanol rather than the *N*-methylamine residue (pK_a 30–40)[12] was deprotonated by *n*-BuLi to result in NMAP siloxide anion (NMAP-Li). Formation of the siloxide anion was indicated by the disappearance of red colour of the complex of 2,2′-bipyridyl with *n*-BuLi. This observation also indicated the absence of lithium amide residue on the silica gel surface (Scheme 3).



Scheme 3. Heterogeneous siloxide anion (NMAP-Li) on reversed phase silica gel (NMAP).

Table 1. Investigation of a base for the domino Michael reaction of oxophorone **4** with cyclohexyl acrylate **3** leading to **7**

Entry	Base	Yield (%)[a]
1	LDA	92[5]
2	Silica gel[c]	90
3	Silica gel/HMPA[b,c]	89
4	NMAP/HMPA[b,c]	90
5	Ph_3SiOH/HMPA[b,c]	97

[a] Yields were for isolated pure product **7** based on oxophorone **4**.

[b] Amount of HMPA was 0.4 equiv to oxophorone **4**.

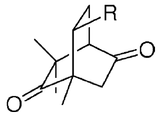
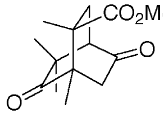
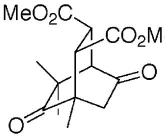
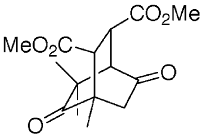
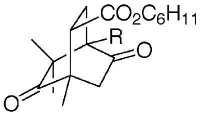
[c] The base was generated from silica gel with 0.1 equiv of *n*-BuLi at 0 °C in the presence of 2,2′-bipyridyl. Consumption of *n*-BuLi was confirmed by the disappearance of red-colour of *n*-BuLi–2,2′-bipyridyl complex. The reaction was carried out at −70 °C to room temperature for 11–18 h.

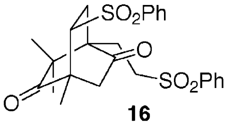
Optimum reaction conditions were examined employing oxophorone **4** (R = H) with cyclohexyl acrylate **3** (EWG = $CO_2C_6H_{11}$) in the presence of various bases generated from silica gel and 0.1 equiv of *n*-BuLi. The results are shown in Table 1. The reaction was catalyzed by either normal phase silica gel anion (entry 2) as well as NMAP anion (NMAP-Li) (entry 4). Reactivity of the bases are almost the same as that of LDA.[5] Owing to higher chemical stability of NMAP than that of normal phase silica gel under the basic reaction conditions, pellets of NMAP were used for further reactions. The catalytic activity of the siloxide anion as the base was indicated by the homogeneous base generated from triphenylsilanol (entry 5, Table 1).

Generality of the present protocol is illustrated in Table 2 employing a combination of oxophorone and its derivatives **4** with various Michael partners **3**.

Acrylonitrile **3** was a very active Michael partner (entry 2, Table 2), though 4.8 equiv were required for complete consumption of oxophorone **4**, probably as a result of graft of acrylonitrile **3** on the silica gel surface. Actually, the amount of acrylonitrile **3** could be reduced to 2.4 equiv when recycled NMAP was employed. The reaction with phenylvinylsulfone was accompanied by the bis-adduct **16** in 10% yield (entry 3). Addition of HMPA was important in some cases, since in the absence of HMPA the bicyclic compound **11** could not be obtained (entry 4) and the yield of **15** decreased to 34% (entry 10), respectively. In the reaction with dimethyl maleate **3**, the *trans*-diester **12** was obtained as a single diastereomer (entry 5 and 6), which clearly indicates that the present reaction proceeded via a successive domino Michael pathway. With dimethyl fumarate **3**, the reaction was accompanied by diastereomer **12** in 15% yield (entry 7). The relative stereochemistries of the products **8**–**16** were confirmed by comparison of NMR spectra with previously reported data.[5] Predominant formation of compound **13** in entry 7 was unexpected, since an electron-withdrawing group always oriented *syn* to a methylene group as shown in the struc-

Table 2. Domino Michael reaction of oxophorone **4** with various Michael partners **3**

Entry	Enone **4**	HMPA[b] (equiv)	Product	Yield (%)[a]
				
1	R = H	0.4	**8** (EWG = $CO_2C_6H_{11}$)	90
2	R = H	—	**9** (EWG = CN)	100
3	R = H	—	**10** (EWG = SO_2Ph)	36
4	R = H	0.5	 **11**	83
5[c]	R = H	1	 **12**	72
6[c]		0.5		53
7[d]	R = H	1	 **13**	55[e]
				
8	R = Me	0.5	**14**	54
9	R = allyl	0.4	**15**	75
10		—		34



16

[a] Yields were for isolated pure product based on oxophorones **4**.

[b] The amount is based on oxophorones **4**.

[c] Dimethyl maleate was employed as a Michael partner.

[d] Dimethyl fumarate was employed as a Michael partner.

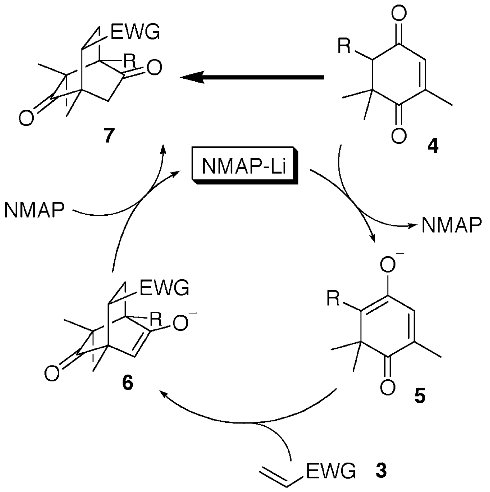
[e] Compound **13** was accompanied by the diastereomer **12** in 15% yield.

Table 3. Recycle of NMAP pellets in the catalytic domino Michael reaction leading to **8**

Entry[a]	Yield (%)[b]
1	75
2	90
3	93
4	94
5	83
6	82

[a] All reactions were carried out with oxophorone **4** and cyclohexyl acrylate **3** with NMAP-Li generated from recovered NMAP and *n*-BuLi (0.2 equiv) in THF.

[b] Yields were for isolated pure product **7** based on oxophorone **4**.



Scheme 4. Domino Michael reaction catalyzed by NMAP-Li as a Brönsted base.

tures of compounds **8**–**12** and **14**–**16**. Compound **12** did not isomerize into **13** by the treatment with LDA at room temperature. Stereochemical outcome in entry 7 is yet to be discussed.

The NMAP pellets were easily recovered, washed with diethyl ether, evacuated and successively reused intact five times without deterioration as shown in Table 3.

Based on these results and discussions, the following catalytic cycle is drawn for the present reaction (Scheme 4). Though pK_a of silica gel is 4.5, there might be silanols having different acidity on the surface of NMAP. Its conjugate base might have variable basic sites which can generate the enolate **5**. After the domino Michael reaction, the resulting bicyclic enolate **6** deprotonates NMAP to regenerate NMAP-Li due to higher acidity of NMAP than that of oxophorone **4**.[13] Thus, it is reasonable to postulate that the present reaction proceeds via NMAP-Li catalysis, not via an autocatalytic pathway in Scheme 2.

In order to investigate the effect of silica gel surface on the reaction, right-handed helical silica gel was employed for an attempted asymmetric induction. However, the reaction with 2-naphthyl acrylate **3** provided the racemic **7** (EWG = CO_2-2-naphthyl) in 53% yield.

In summary, we have developed a new heterogeneous Brønsted base, NMAP-Li, generated from NMAP and *n*-BuLi, which effectively catalyzed the domino Michael reaction of oxophorone and its derivatives **4** with various Michael partners **3** to provide the bicyclo[2.2.2]-octane-2,5-dione derivatives **7**.[14,15] The catalytic activity and the product distribution by NMAP-Li in the present reactions were comparable to LDA.[5] The NMAP was reused up to six times in 86% average yield. To the best of our knowledge, this is the first example that silica gel anion played a role as a Brønsted base to catalyze nucleophilic reaction.

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13. pK_a Values of oxophorones **4** (R = H and R = Me) in water were estimated by a semiempirical method to be 9.18 and 10.38, respectively. We appreciate Dr. Naoto Okuyama, Daicel Chemical Industries, for the calculation.
14. Typical experimental procedure: NMAP pellets were irradiated microwave for 30 s and evacuated 5 min under reduced pressure. The sequence was repeated three times before use. To a stirred suspension of NMAP pellets (106 mg) in THF (0.5 mL) was added a solution of 2,2′-bipyridyl (6.7 mg, 0.043 mmol) in THF (0.25 mL) and subsequently *n*-BuLi (60 μL, 1.59 M solution in *n*-hexane, 0.043 mmol) at 0 °C under nitrogen atmosphere. The purple solution became pale yellow in 30 min. After being stirred for further 15 min, a solution of oxophorone **4** (R = H) (64 mg, 0.43 mmol) in THF (0.8 mL) was added to the suspension at −70 °C. After being stirred for 45 min at the temperature, HMPA (30 μL, 0.17 mmol) and subsequently cyclohexyl acrylate **3** ($EWG = CO_2Cy$) (80 μL, 0.51 mmol) were added. The reaction temperature was allowed to rise to room temperature for 17 h. The supernatant was transferred to a separatory funnel. The NMAP was rinsed with ethyl acetate. The combined organic layer was washed with dil. HCl, water, brine and dried over anhydrous sodium sulfate. The organic layer was evaporated to dryness and the residue was purified by medium-pressure LC (eluent: ethyl acetate:*n*-hexane = 1:3) to give the product **7** (115 mg, 90%). The NMAP was dried according to the procedure cited above for subsequent use.
15. Other efforts to prepare **7** by domino Michael protocol: Albrecht, H.; Dietz, M.; Schon, C.; Baumann, V. *Synthesis* **1991**, 133; Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999.