Auto-tandem catalysis: facile synthesis of substituted alkylidenecyclohexanones by domino (4 + 2) cycloaddition–elimination reaction†

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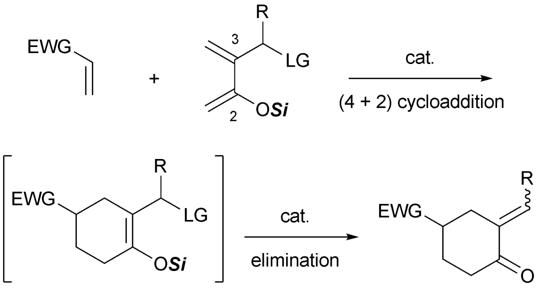
A catalytic domino reaction producing substituted 2-alkylidenecyclohexanone from 3-oxymethyl-2-siloxy-1,3-butadienes, which can be prepared from Baylis–Hillman adducts, and α,β-unsaturated ketones is described. The process involves two mechanistically distinct reactions, (4 + 2) cycloaddition and elimination. Both of these reactions are catalyzed by Tf_2NH.

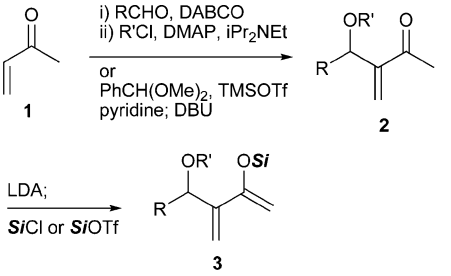
Domino (cascade) reactions, where multiple chemical transformations proceed in one sequence without isolation of intermediates, represent efficient, economic and ecological processes in organic synthesis.[1] The catalytic variants have also been receiving a great deal of attention as powerful and useful methods for several reasons, including atom economy, energy-efficiency and reaction diversity controlled by the catalyst. As a related chemistry, auto-tandem catalysis has received a great interest in synthetic efficiency.[2] The term 'auto-tandem catalysis' is defined as one catalyst which promotes two or more mechanistically distinct reactions in a domino process. Recently, we have reported auto-tandem catalysis of acid catalysts in domino (4 + 2)–(2 + 2) cycloaddition producing bicyclo[4.2.0]octanes.[3,4] In the domino process, both of the (4 + 2) and (2 + 2) cycloadditions are activated by the same catalyst, such as $EtAlCl_2$ and triflic imide (Tf_2NH).[5] During the course of our continuous study to develop new transformation reactions, we have found a novel auto-tandem catalysis in which Tf_2NH independently catalyzes both (4 + 2) cycloaddition and elimination reactions. Thus, the cycloaddition of 2-siloxydienes bearing a hydroxymethyl substituent at 3-position with enones, followed by elimination of the generated 2-oxymethyl-1-siloxycyclohexenes, afforded 2-alkylidenecyclohexanones, *exo*-enones (Scheme 1). *exo*-Enones are versatile synthetic substrates in organic synthesis, such as dienophiles in Diels–Alder reaction, Michael acceptors and oxa-dienes in hetero Diels–Alder reaction.[6] Moreover, compounds possessing *exo*-enone moiety have attracted attention as potential drug candidates to show various biological activities, such as antitumor and antiviral effects.[7] We wish to report herein a new auto-tandem catalysis producing substituted *exo*-2-alkylidenecyclohexanones.



Scheme 1 Domino (4 + 2) cycloaddition–elimination reaction.

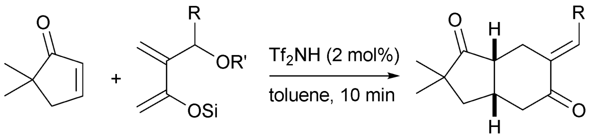
3-Oxymethyl-2-siloxybutadienes **3** were prepared easily from methyl vinyl ketone (MVK, **1**) utilizing the Morita–Baylis–Hillman reaction (Scheme 2).[8] Namely, the reaction of **1** and aldehydes in the presence of diazabicyclooctane (DABCO) followed by protection of the generated hydroxyl group, afforded enones **2**. Treatment of **2** with silyl chloride or triflate in the presence of triethylamine furnished 2-siloxydienes **3**. 3-Methoxymethyl-2-siloxybutadienes **3f** and **3j** were prepared from benzaldehyde dimethyl acetal according to the reported procedure by Kim *et al.*[9]

With the substrates in hand, the Tf_2NH-catalyzed reaction of **3** with enone **4** was explored first (Scheme 3). When 2 mol%



	R	R'	*Si*		R	R'	*Si*
3a	H	TBS	TMS	**3f**	Ph	Me	TES
3b	H	TBS	TES	**3g**	Ph	MOM	TES
3c	H	TBS	TBS	**3h**	Ph	Bz	TES
3d	Ph	TES	TES	**3i**	Me	TES	TES
3e	Ph	TMS	TES	**3j**	$^{p}BrC_6H_4$	Me	TES

Scheme 2 Synthesis of 3-oxymethyl-2-siloxydienes.



Scheme 3 Catalytic domino reaction of **3** and **4**.

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Table 1 Effects of silyl group and reaction temperature[a]

			% Yield	
Entry	**3** (*Si*, R, R′)	Temperature/°C	**5a**[b]	**2a**[b]
1	**3a** (TMS, H, TBS)	–40	31	14
2	**3b** (TES, H, TBS)	–40	53	9
3	**3c** (TBS, H, TBS)	–40	66	8
4	**3c**	–60	0	Trace
5	**3c**	0	47	20

[a] Conditions: **3** (1.2 equiv.), **4a** (1.0 equiv.), Tf_2NH (2 mol%), toluene, 10 min. [b] Yields of **5** and **2** were calculated based on **3**.

Table 2 Effects of leaving group[a]

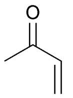
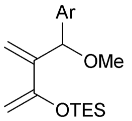
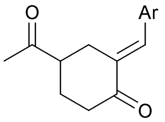
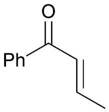
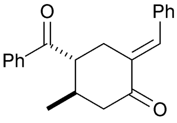
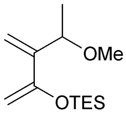
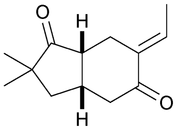
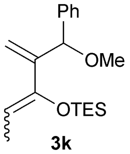
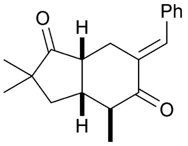
			% Yield	
Entry	**3** (*Si*, R, R′)	Solvent	**5b**[b]	**6**[b]
1	**3d** (TES, Ph, TES)	Toluene	66	0
2	**3e** (TES, Ph, TMS)	Toluene	58	0
3	**3f** (TES, Ph, Me)	Toluene	66	0
4[c]	**3g** (TES, Ph, MOM)	Toluene	13	28
5[e]	**3g**	Toluene	48	0
6[d]	**3h** (TES, Ph, Bz)	Toluene	0	0
7[e]	**3d**	Toluene	78	0

[a] Conditions: **3** (1.2 equiv.), **4a** (1.0 equiv.), Tf_2NH (2 mol%), toluene, −40 °C, 10 min. [b] Yields of **5** and **6** were calculated based on **3**. [c] 18% of **3g** was recovered. [d] 92% of **3h** was recovered. [e] **3d** (2.0 equiv.) and Tf_2NH (10 mol%) were used.

of Tf_2NH was treated with a mixture of **3a** (Si = TMS) and 5,5-dimethylcyclopenten-2-one (**4a**) in toluene at −40 °C, **3a** was completely consumed within 10 min to give 2-methylene-cyclohexanone **5a** in 31% yield along with **2a** (Table 1, entry 1). We considered that decomposition of **3a** into **2a** by desilylation would be caused by the weakness of its silyl–oxygen bond. The chemical yield of **5a** was improved, as expected, when the reaction performed with **3b** and **3c** bearing more bulky silyl groups, TES and TBS, respectively (entries 2 and 3). Reaction at 0 °C afforded **5a** in moderate yield (entry 5). On the contrary, no cycloaddition proceeded at −60 °C (entry 4). These results indicate that promotion of cycloaddition requires more than *ca* −40 °C, but decomposition of **3** increases at higher temperatures.[10] No silyl enol ether **6a** was detected on TLC and NMR in the reaction of **3a–c**.

Next, the effects of the leaving group of **3** (R′O) were examined (Table 2). Siloxy and methoxy substituents show good leaving ability in the domino reaction (entries 1–3). Reaction of substrate **3g** having methoxymethyl (MOM) group with **4a** furnished the desired **5g** in 13% yield along with silyl enol ether **6g** in 28% yield (entry 4). The reaction cascade was completed within 10 min by using 10 mol% of Tf_2NH (entry 5). We have considered that the domino reaction involves an auto-tandem catalysis in which Tf_2NH activates both (4 + 2) cycloaddition and elimination. It was also made clear that the desilylative elimination of **6g** (R = Ph, R′ = MOM, Si = TES) was promoted by the assistance of the catalyst. In the absence of Tf_2NH, no formation of enone **5g** from **6g** was observed at −40 °C. On the other hand, **5g** was quantitatively obtained within 1 h when **6g** was treated with 10 mol% of Tf_2NH at the same temperature. Decomposition of siloxydiene **3** was detected in all of the reactions tested. No cycloaddition of benzoate **3h** with **4a** occurred under the same conditions (entry 6). Finally, the chemical yield of **5** could be improved to 78% when an excess amount (2.0 equiv.) of substrate **3d** was employed in the presence of 10 mol% of Tf_2NH (entry 7).[11] It is noteworthy that the chemical yield would be not too dependent on the R substituent of the substrate.

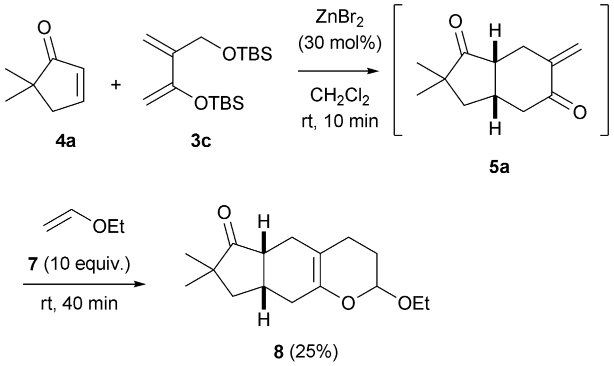
Table 3 Synthesis of substituted alkylidenecyclohexanones by domino (4 + 2) cycloaddition–elimination reaction[a]

Entry	Enone	Siloxydiene	Product	% Yield of **5**
1 2	 **1**	 **3f** (Ar = Ph) **3i** (Ar = $^{p}BrC_6H_4$)		76 68
3[b]	 **4b**	**3f**		50 (single diastereomer)
4	**4a**	 **3i**		51
5 6	**4a** **4a**	 *Z* : *E* = 20 : 80 *Z* : *E* = 75 : 25 **3k**		46 (single diastereomer) 49 (single diastereomer)

[a] Conditions: **3** (2.0 equiv.), **1** or **4** (1.0 equiv.), Tf_2NH (10 mol%), toluene, −40 °C, 10 min. [b] **3f** (1.5 equiv.) was used.

Optimal conditions in hand, synthesis of several alkylidenecyclohexanones by the domino reaction was explored (Table 3). Substituted *exo*-enones **5c–5g** were obtained in moderate to good yields. *trans*-β-Substituted enone **4b** afforded cycloadduct **5e** as a single diastereomer, whose stereochemistry at the C(4) and C(5) substituents was assigned to be *anti* (entry 3). It is noteworthy that both geometrical isomers of 2-siloxybutadiene **3k** bearing a methyl substituent at the C(1) position afforded **5g** as a single diastereomer (entries 5 and 6). The observation suggests that the cyclization occurs *via* a stepwise double Michael pathway rather than a concerted Diels–Alder reaction.[12,13] Stereochemistry of all the products was determined by ^{1}H NMR (*J* values) and NOESY experiments.

Next, we assessed an oxa Diels–Alder reaction of *exo*-enone **5** to develop a new auto-tandem catalysis in domino reaction. No cycloadduct was obtained when **5a** was treated with ethyl vinyl ether (**7**) in the presence of Tf$_2$NH. In contrast, when ZnBr$_2$ was employed as a catalyst, tricyclic dihydropyran **8** was obtained from **5a** as a single diastereomer. When a solution of ZnBr$_2$ (30 mol%) was added to an equimolar mixture of **3c** and **4a** at ambient temperature, followed by treatment with excess amounts of **7**, tricyclic compound **8** was obtained in 25% yield as a single diastereomer (its stereochemistry was not determined). Albeit a low conversion, it was clear that in the domino process the catalyst activates three different reactions: (4 + 2) cycloaddition, elimination and the hetero Diels–Alder reaction (Scheme 4).



Scheme 4 One-pot synthesis of tricyclic acetal of **8** by a domino (4 + 2)-cycloaddition–elimination–oxa Diels–Alder reaction.

In summary, we have developed a new catalytic domino reaction producing substituted 2-alkylidenecyclohexanones from 3-oxymethyl-2-siloxydienes and α,β-unsaturated ketones. We consider that our developed reaction giving *exo*-cyclohexenones from 3-oxymethyl-2-siloxydienes would be complementary to the reaction of Danishefsky's diene (1-methoxy-3-siloxydiene) to afford *endo*-cyclohexenones.[14] It is noted that the catalytic domino reaction includes an auto-tandem catalysis in which Tf$_2$NH independently catalyzes a stepwise (4 + 2) cycloaddition and elimination reactions.

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10 Effects of solvent and catalyst were examined. CH$_2$Cl$_2$ and toluene were optimal solvents. In contrast, chemical yields of **5** decreased in polar solvents such as CH$_3$CN. Several Lewis acids such as BF$_3$–OEt$_2$, ZnBr$_2$, ZnI$_2$ and EtAlCl$_2$ promoted the domino reaction, although 20–100 mol% of the catalyst was required to complete the reaction (see ESI†).

11 Representative procedure: to a solution of **3d** (0.40 mmol) and **4a** (0.20 mmol) in toluene (1.5 mL) was added a solution of Tf$_2$NH (20 μmol) in toluene at −40 °C. After stirring for 10 min, the mixture was quenched with NEt$_3$ (approximately 0.1 mmol) at the same temperature. Concentration of the resulting mixture, followed by column chromatography on silica gel (AcOEt : hexane = 10 : 90), furnished **5b** (42 mg, 78% yield) as colorless solids. Spectral data for **5b**; mp 78–79 °C, IR (neat): 3058, 2961, 1742, 1687 cm^{-1}, ^{1}H NMR (CDCl$_3$, 400 MHz) d: 7.61 (1H, s), 7.41–7.33 (5H, m), 3.11–2.75 (5H, m), 2.46 (1H, dd, *J* = 14.6, 6.1 Hz), 2.14 (1H, dd, *J* = 13.2, 7.3 Hz), 1.42 (1H, dd, *J* = 13.2, 9.8 Hz), 1.08 (3H, s), 1.05 (3H, s), ^{13}C NMR (CDCl$_3$, 125 MHz) d: 222.1, 200.4, 136.3, 134.8, 133.1, 129.8, 128.8, 128.5, 45.9, 44.2, 43.3, 42.8, 28.5, 24.9, 24.7, 22.9, HRMS (FAB$^+$) calcd for $C_{18}H_{19}O_2$ $(M - H)^+$: 267.1380, found: 267.1380.

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