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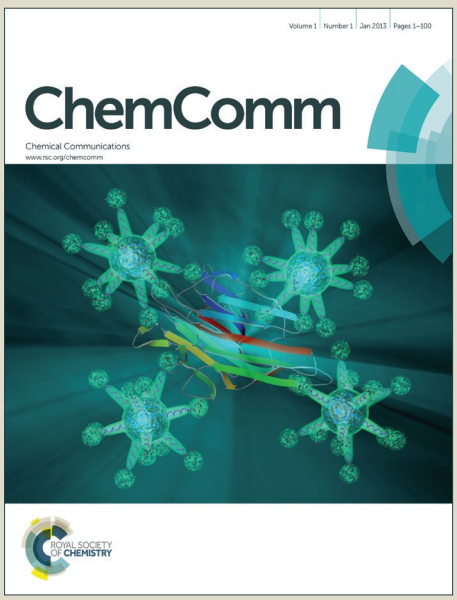

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Sequential Mukaiyama–Michael reaction induced by carbon acids

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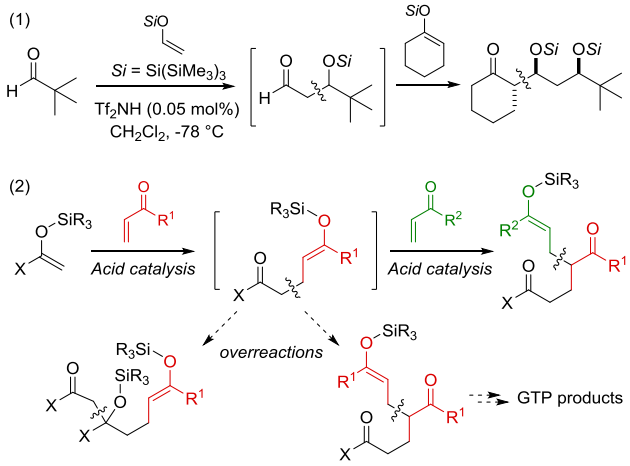
In the presence of strong carbon acid, sequential Mukaiyama–Michael reaction using two different Michael acceptors proceeded; the reaction of ketene silyl acetal derived from EtOAc with α-pyrones as primal acceptors yielded the corresponding cyclic ketene silyl acetals, which were enough reactive to undergo the following reaction with second acceptors.

Discovery of the Mukaiyama aldol reaction in 1973 has motivated further investigations on organic reactions using silicon enolates such as enol silyl ethers (ESEs) and ketene silyl acetals (KSAs) until today.[1] In particular, sequential reactions using silicon enolates recently attract much attention to construct complex molecular architecture in a one pot manner. For example, Yamamoto reported sequential Mukaiyama aldol reaction using tris(trimethylsilyl)silyl enol ethers (Eqn. 1).[2] In the presence of Tf_2NH (Tf = SO_2CF_3), the reaction of aldehyde with the ESE produced β-silyloxyaldehyde, which could be subjected in one pot to the second Mukaiyama aldol reaction with another ESE. The 1,4-addition of silicon enolates to α,β-unsaturated carbonyls, so-called the Mukaiyama–Michael reaction, is also a fundamental method for C–C bond formation.[3] However, its sequential version using two or more different Michael acceptors is not common (Eqn. 2).[4,5] The difficulties come from undesired overreactions of the intermediates, which possess both of the nucleophilic ESE or KSA moiety and the electrophilic carbonyl moiety, with the unreacted Michael acceptors or nucleophilic species. If the *in situ*-generated silicon enolates have higher nucleophilicity than the starting one, competitive polymerization of the Michael acceptor will occur. Actually, group transfer polymerization (GTP) of (meth)acrylic acid esters using KSAs as initiators is a well-established living polymerization technique.[6,7] In addition, some successful examples of the sequential reactions initiated by the Mukaiyama–Michael reaction suggest that intramolecular trapping of the intermediates is necessary to obtain the desired products.



The (4+2)[8] or (2+2)[9] cycloadditions of silicon (di)enolates with α,β-unsaturated carbonyls are categorized into such reaction systems. Herein we describe that, by using strongly acidic carbon (C–H) acid catalysts,[10] the sequential, one-pot reactions triggered by the Mukaiyama–Michael reaction occur in a controlled manner; the carbon acid nicely promoted the 1,4-addition of a KSA to α,β-unsaturated lactones giving rise to the corresponding cyclic KSA intermediates, which were enough reactive to be engaged in the following the Mukaiyama aldol or Mukaiyama–Michael reaction.

In designing desired sequential reactions triggered by the Mukaiyama–Michael reaction, we referred to the Mayr's nucleophilicity parameter *N* as a guiding principle.[11] The *N* value of **A**, a KSA derived from butyl acetate, is higher than that of **C** derived from acetone (Figure 1). More importantly, the value of phenylated derivative **B** lies midway between **A** and **C**. Keeping this in mind, we first examined the reaction of isocoumarin **3a**, which was a cyclic analogue of phenyl acrylate, with a KSA **4** derived from ethyl acetate in the presence of triple carbon acid **1a** (Eqn. 3).[12] In previous work,

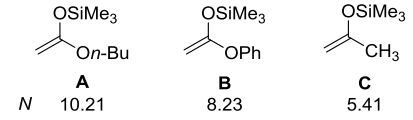


Fig 1 Mayr's nucleophilicity parameters *N* of some silicon enolates

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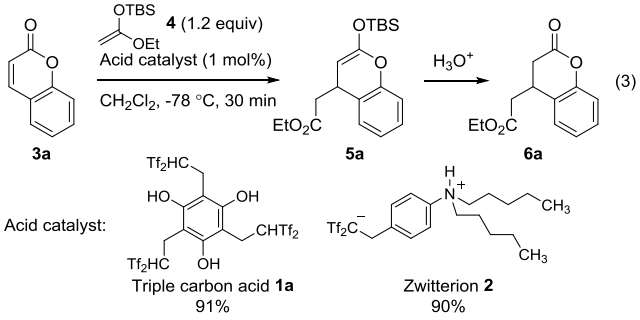
this acid demonstrated higher catalytic activity over usual acids such as TfOH and Tf_2NH in some C–C bond forming reactions. Upon treatment with 1.2 equiv of the KSA and 1 mol% of **1a** at –78 °C, **3a** was rapidly consumed to give the Mukaiyama–Michael product **6a** in 91% yield after acidic workup. ^{1}H NMR analysis revealed quantitative formation of the intermediate **5a** before the workup. Similar result was obtained by using zwitterion **2**[13] instead of **1a**. Unfortunately, 5,6-dihydro-2*H*-pyran-2-one just gave a complex mixture and phenyl acrylate did not react with **4**.[14]

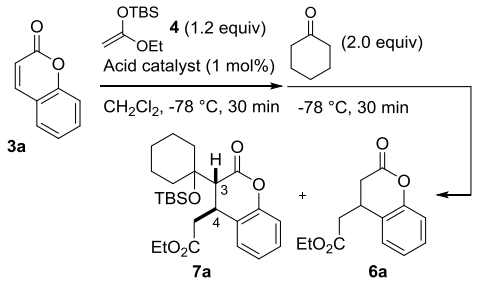


Next we tried trapping the *in situ*-generated KSA **5a** with cyclohexanone as the second electrophile (Table 1).[15] When the reaction mixture obtained from **3a** and **4** was treated with 2.0 equiv of cyclohexanone in a one pot manner, the desired reaction took place to give 3,4-*anti* product **7a** in 99% yield (entry 1). Under similar conditions, lower loading of **1a** resulted in selective formation of simple Mukaiyama–Michael product **6a** along with recovery of a small amount of **3a** (entry 2). This indicated that carbon acid **1a** promoted not only initial Mukaiyama–Michael step but also the following Mukaiyama aldol reaction with cyclohexanone. In this case, less acidic zwitterion **2** was ineffective (entry 3). $Tf_2CHCH_2CHTf_2$ **1b**, $Tf_2CHC_6F_5$ **1c**, and Tf_2NH could be used, while a considerable amount of **6a** was also obtained (entries 4-6). In contrast, TfOH and some Lewis acids such as $Ph_3C^+PF_6^-$ and TBSOTf did not show acceptable catalysis (entries 7-9).

As shown in Figure 2, under the optimized conditions, cyclopentanone and acetone were found to be excellent as the second electrophile (**8a**, 87% yield; **9a**, 97% yield). Likewise, 2-methylcyclohexanone gave the product **10a** in 82% yield as a mixture of two diastereomers in a ratio of 8.1:1.[16] Substituted isocoumarins **3b**-**3e** reacted cleanly as the primal electrophile to yield the corresponding products **9b**-**9e** with perfect 3,4-*anti* selectivity by the trapping with acetone. α-Pyrones **3f** and **3g** also worked well and the desired products **9f** and **9g** were isolated in 90% and 87% yields, respectively. Here it should be noted that acid-sensitive vinyl ester moiety of these products were tolerant to acid **1a**.

Next, we conducted the reactions with α,β-unsaturated ketones as the second Michael acceptor (Figure 3). Our initial effort using isocoumarin **3a** and methyl vinyl ketone, as the primal and second Michael acceptors, respectively, gave the desired product **11a** in 59% yield without any overreactions (**6a** was also isolated in 21% yield). Under the similar conditions, phenyl vinyl ketone was a better reaction partner. For instance, the reaction of **3a**, **4**, and phenyl vinyl ketone gave the desired 3,4-*anti* product **12a** in 83% yield after desilylation with TfOH. Mesityl oxide also worked as second acceptor to give **13a** in 61% yield with the Mukaiyama aldol product (not

Table 1 Effects of acids in sequential Mukaiyama–Michael/Mukaiyama aldol reaction



Entry	Acid catalyst	Yield[a] (%) 7a	6a	Recovery of 3a[a] (%)
1	Carbon acid **1a**	99	0	0
2[b]	Carbon acid **1a**	2	68	19
3[c]	Zwitterion **2**	4	87	0
4[d]	$Tf_2CHCH_2CHTf_2$ **1b**	87	<5[e]	0
5[c]	$Tf_2CHC_6F_5$ **1c**	69	11[e]	0
6[c]	Tf_2NH	59	12[e]	0
7	TfOH	0	7[e]	87
8	$Ph_3C^+PF_6^-$	13	37	14
9	TBSOTf	3	40	52

[a] Isolated yield. [b] 0.25 mol% of acid was used.
[c] 3 mol% of acid was used. [d] 1.5 mol% of acid was used.
[e] Determined by ^{1}H NMR of crude mixture.

shown) in 12% yield. By using phenyl vinyl ketone as the second acceptor, the reactions of substituted isocoumarins **3b**-**3e** as the first ones were examined. In all cases, the desired products **12b**-**12e** were isolated in good to excellent yields. Likewise, the sequential reaction of α-pyrones **3f** and **3g** was successful; the corresponding products **12f** and **12g** were obtained in 84% and 72% yields, respectively. Cyclic enones were also suitable second Michael acceptors. 5-, 6-, and 7-Membered enones smoothly reacted with KSA **5a** generated from **3a**

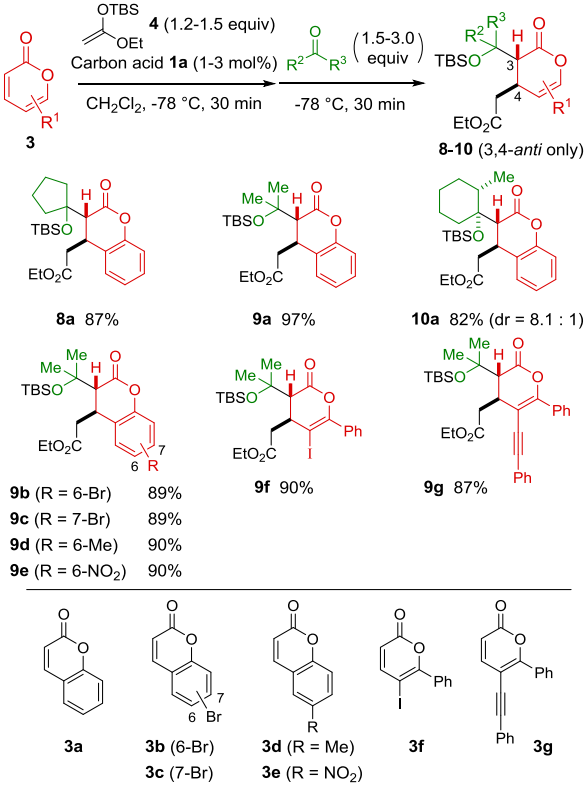


Fig 2. Sequential Mukaiyama–Michael/Mukaiyama aldol reaction

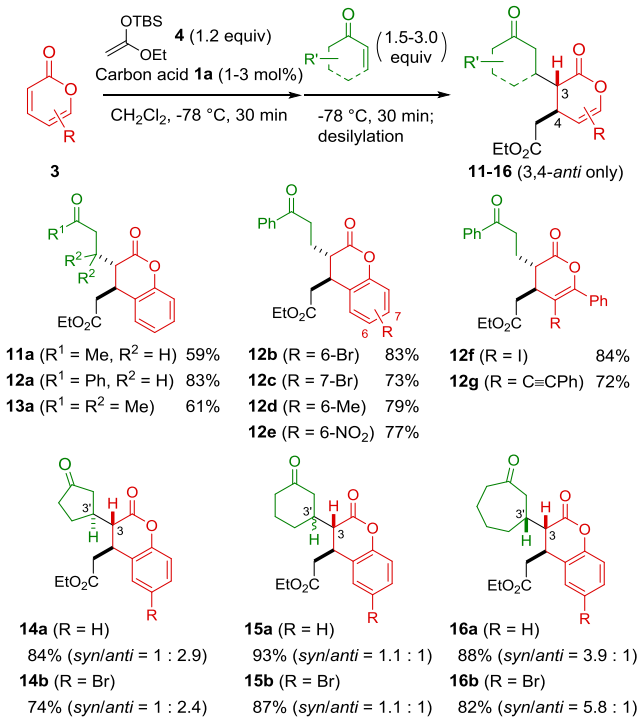
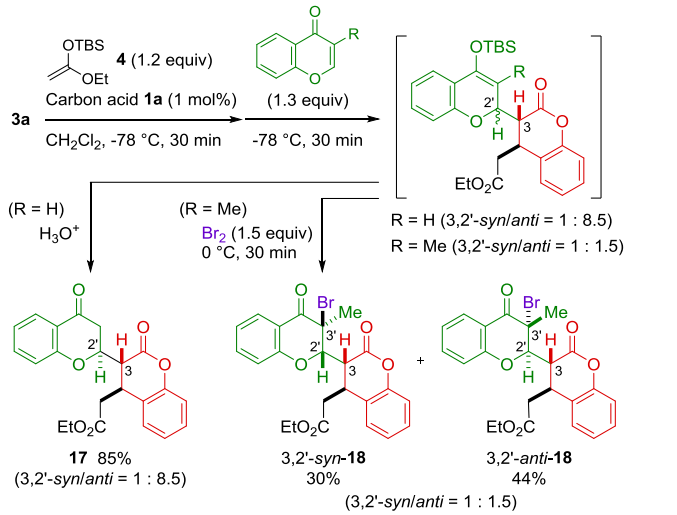
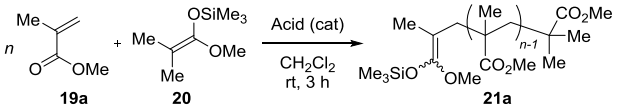


Fig 3. Sequential Mukaiyama–Michael reaction



Scheme 1. Further reactions of sequential Mukaiyama–Michael products

Table 2 GTP of methyl methacrylate **19a**[a]



Entry	Acid (equiv)	Conversion of **19a**[b] (%)	$M_{n(SEC)}$[c] (g mol^{-1})	M_w/M_n[c]
1	$Tf_2CHCH_2CHTf_2$ **1b** (0.02 equiv)	>99	11,300	1.04
2	Carbon acid **1a** (0.05 equiv)	<1	--	--
3	Zwitterion **2** (0.05 equiv)	<1	--	--

[a] Ar atmosphere; **19a**/**20**/Acid = 100 : 1 : 0.02-0.05, [**19a**]$_0$ = 1.0 mol L^{-1}. [b] Determined by ^{1}H NMR in $CDCl_3$. [c] Determined by size exclusion chromatography (SEC) in THF using poly(methyl methacrylate) standards.

to be converted to the ketones **14a**-**16a** in excellent yields with moderate to good diastereoselectivity. Under the similar conditions, the sequential Mukaiyama–Michael products **14b**-**16b** were isolated by the reaction of 6-bromoisocoumarin **3b**. In these cases using cyclic enones, the perfect 3,4-*anti* selectivity was preserved and only two diastereomers (3,3'-*syn* and *anti*) were obtained.

We also found that the sequential Mukaiyama–Michael reaction nicely proceeded with chromones as the second Michael acceptors (Scheme 1). For example, the reaction of **3a**, **4**, and chromone itself produced the corresponding ketone **17** in 85% yield as a 1:8.5 mixture of 3,2'-*syn*- and *anti*-diastereomers after acidic workup. This diastereoselectivity closely reflected the ratio of the ESE intermediate. Although bromination was possible by treating this ESE intermediate with bromine at 0 °C, isolation and characterization of the desired α-bromoketone failed due to its rapid epimerization during purification. On the other hand, bromination of the ESE derived from 3-methlychromone proceeded in a 2',3'-*anti* manner to give only two products 3,2'-*syn*-and 3,2'-*anti*-**18** in 30% and 44% yields, respectively. This is a rare example of four-component bond forming reaction in a linear fashion using one reaction vessel.

The present results suggested that unexpected low catalytic activity of triple carbon acid **1a** in any GTP, even though Tf_2NH and $Tf_2CHC_6F_5$ **1c** served as effective catalysts for the GTP of (meth)acylate derivatives.[17] To confirm this point, we evaluated catalytic activity of carbon acids **1a**, **1b** and zwitterion **2** in the GTP of methyl methacrylate **19a** and butyl acrylate **19b** with KSA **20** (Table 2 and ESI). In the presence of 0.02 equiv of **1b**, the GTP of **19a** produced well-controlled polymer **21a** with M_w/M_n of 1.04 and $M_{n(SEC)}$ of 11,300, which corresponded to $M_{n(calcd)}$ of 10,100 (entry 1).[18] In contrast, any polymers were not obtained by using even 0.05 equiv of triple carbon acid **1a** (entry 2). Furthermore, zwitterion **2** did not work as an acceptable catalyst (entry 3).

Regarding catalytic pathway for the sequential Mukaiyama–Michael reaction, we propose the *in situ*-generated silicon Lewis acid as a catalytically active species (Figure 4).[19] That is, loosely contact ion pair **D** is generated by protonation of starting KAS **4** by triple carbon acid **1a** and it activates the primal Michael acceptor **3** through *O*-silylating reaction giving rise to the intermediate **E** and ethyl acetate. In this context, ion pair **D** can be depicted as an equivalent of Lewis acid "R_3Si^+". Recent theoretical study on the conjugate base [**1a**]$^-$ of the acid **1a** confirmed its unexpected stability through two-point hydrogen bonding between sulfonic oxygens and proximal phenolic hydroxyl groups on the benzene ring.[20] Therefore, it would be unlikely to generate the *C*-silylated species through further attack of [**1a**]$^-$ on the silicon atom. The following nucleophilic attack of unreacted **4** on **E** produces the intermediate **F**. After that, silyl transfer reaction from **F**, which also works as the "R_3Si^+" equivalent, to unreacted acceptor **3** results in regeneration of **E** along with formation of the 1,4-adduct **5** bearing silicon enolate moiety. In the sequential reaction, the second Michael acceptor is activated in a similar way by "R_3Si^+" equivalents existing in the reaction system. In our case, no overreactions were observed. The present outcome can be rationalized by considering relative nucleophilicity of each silicon enolates. As mentioned above, we carefully chose each Michael acceptors on the basis of the Mayr's nucleophilicity, which was determined by reaction rate of silicon enolates with stabilized carbocations.[11] To avoid undesired overreactions including the GTP, it is necessary to evaluate the nucleophilicity of each intermediates

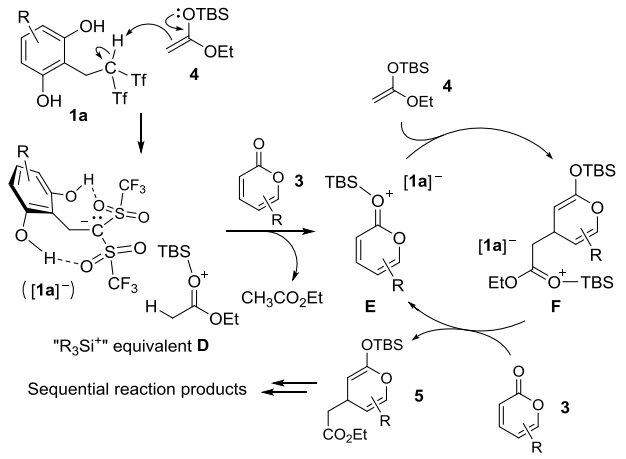


Fig 4. Plausible reaction pathway

rigorously. Our results demonstrate that the Mayr's nucleophilicity *N* is helpful as a practical guiding principle for such sequential reaction systems. The nucleophilicity of **5**, which is generated by the primal Mukaiyama–Michael reaction, is lower than that of starting one **4** (Figure 4). Therefore, relatively faster reaction rate of activated lactone **E** with **4** over **5** brings about preferential formation of **5**. We managed similar reactivity difference in the second Mukaiyama–Michael reaction by using α,β-unsaturated ketones.

Satisfactory correlation between the nucleophilicity and the reaction outcome in such sequential systems implies that the Michael acceptors, not but the donors, are one-sidedly activated. If "R_3Si^+" equivalents activate the acceptor, at the same time, their counter anions activate the donor through attacking on the silicon atom, we will not find good correlation. Obviously, some features of triple carbon acid **1a**, *e.g.* its low loading and no nucleophilicity of [**1a**]$^-$, work to suppress undesired overreactions. Unexpected lower catalyst activity of **1a** in GTP of methyl methacrylate **19a** would support this thing. Our work suggests that one-sided, strong activation of Michael acceptors becomes a promising approach to such sequential reactions.

In summary, we found that triple carbon acid **1a** was remarkably effective for the 1,4-addition chemistry of silicon enolates. The Mukaiyama–Michael reaction of carboxylic acid derivatives is used as an excellent polymerization method producing well-controlled polymers. In contrast, we successfully arranged some different electrophiles in an order by linear, stepwise bond formations without any overreactions; the results presented herein are the first examples for a practical level of sequential Mukaiyama–Michael reaction using two different α,β-unsaturated carbonyls. The present sequential reactions also provide an effective methodology to make covalent bonds between sterically hindered substrates.

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