Synthetic Methods

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Selective Michael Reaction Controlled by Supersilyl Protecting Group**

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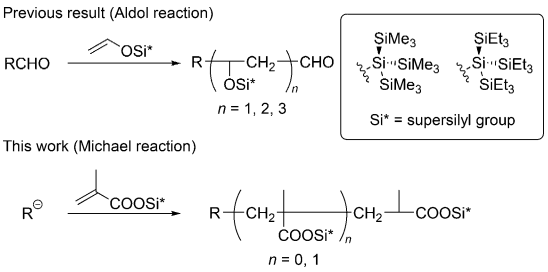
Abstract: *Selective Michael reaction of organolithium reagents to supersilyl methacrylate is reported. The method was able to control a single and double Michael addition. The successful termination of the process using the supersilyl protecting group allows for the controlled, chemoselective, and diastereoselective Michael reaction.*

The conjugate addition reaction between electron-deficient olefins and nucleophiles (commonly referred to as Michael addition reaction) has long been regarded as a powerful tool for organic synthesis for the preparation of materials, natural products, and pharmaceuticals.[1]

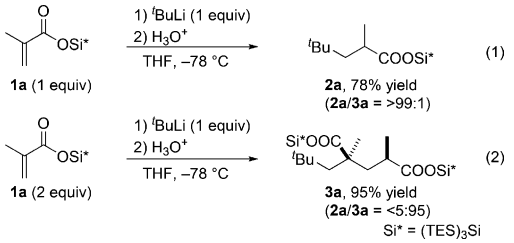
In polymer chemistry, the Michael addition has wide application, e.g., for the anionic polymerization of methyl methacrylate (MMA) with nucleophiles such as alkyllithium.[2] In particular, poly(methyl methacrylate) (PMMA) has been extensively used for a variety of materials that found widespread use in everyday life. In general, a polymer was produced by the reaction of methacrylate esters with alkyllithium or Grignard reagents. It is very difficult to stop this reaction at the desired stage to obtain either the single (1:1) or double (1:2) Michael adduct, because the corresponding intermediates exhibit similar reactivity toward the methacrylate ester.[3] On the other hand, the selective dimer adduct formation was reported only with a bulky α-substituent (trimethylsilyl) on the acrylate moiety.[4] However, to the best of our knowledge, no such example has been reported for methacrylate esters. Thus, achieving the selective formation of single and double Michael addition products using methacrylate ester is a very challenging goal.

Previously, we have reported the successive aldol process to stop at the mono-, di-, and trialdol stage with exceptionally high diastereoselectivities using the tris(trialkylsilyl)silyl (also called "supersilyl") protecting group (Scheme 1).[5] The anionic polymerization of MMA is known to be one of the most popular anionic polymerization processes and herein we will report the successful termination of the process using the supersilyl protecting group[6,7] to generate chemoselective single and double Michael addition products with high diastereoselectivities. The tris(trimethylsilyl)silyl methacrylate (TTMSSMA) was used by Okamoto et al. for the tacticity- and molecular-weight-controlled radical polymerization to generate poly(TTMSSMA).[8]



Scheme 1. Selective reaction controlled by supersilyl protecting group.

Supersilyl methacrylate could be prepared directly from methacrylic acid and tris(triethylsilyl)silyl (TTESS) triflate by our reported method.[6a] We first examined the Michael reaction of supersilyl methacrylate **1a** with ^{t}BuLi in THF at −78 °C for 2 h, after which the reaction was quenched with saturated aqueous NH_4Cl solution, and observed the formation of the 1:1 Michael adduct **2a** in 78% yield [Scheme 2, Eq. (1)].[9] After this time, the expected 1:2 Michael adduct **3a** was not obtained. The use of two equivalents of **1a** resulted in the formation of the 1:2 Michael adduct **3a** in 95% yield as a single diastereomer [Scheme 2, Eq. (2)]. In this case, a small amount of 1:1 Michael adduct **2a** was also obtained (< 5%). The relative configuration of 1:2 Michael adduct **3a** was confirmed by X-ray crystallographic analysis of the dicarboxylic acid **4** obtained by deprotection of the supersilyl protecting group (Figure 1).[10] These Michael reactions using supersilyl methacrylate were realized with excellent chemoselectivity and diastereoselectivity.



Scheme 2. Michael addition of *tert*-butyllithium to supersilyl methacrylate **1a**.

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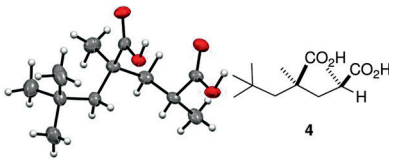
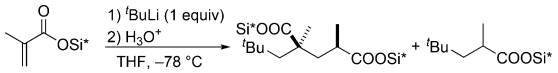


Figure 1. X-ray structure of **4**.

Table 1: Michael addition of supersilyl methacrylate **1a**.[a]



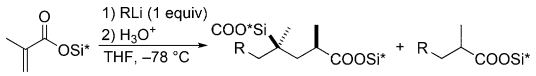
Entry	*x* [equiv]	Yield [%][b]
1	2	92
2	3	82
3	5	68[c]

[a] Reaction conditions: **1a** (*x* equiv), ^{t}BuLi (0.2 mmol) in THF at −78 °C for 2 h. [b] Yield of the isolated product. [c] Three equivalents of starting material **1a** was recovered. Si* = $(TES)_3Si$.

When three and five equivalents of **1a** was used, the 1:2 Michael adduct **3a** was obtained in good yield as a single diastereomer and with excellent chemoselectivity, without the formation of a 1:3 Michael adduct (Table 1, entries 2 and 3). We found that the supersilyl protecting group could stop the polymerization process. In fact, the use of controlled amounts of methacrylate ester resulted in the selective formation of 1:1 and 1:2 Michael adducts.

The substrate scope of lithium regents in this double Michael reaction process was then investigated under the standard reaction conditions for RLi (1 equiv) and **1a** (2 equiv), and excellent chemoselectivities were obtained (Table 2). Ethyllithium and butyllithium gave 1:2 Michael adducts in good yields and low to moderate diastereoselectivities (entries 1 and 2). The use of isopropyllithium afforded the 1:2 Michael adduct with good yield and good diastereoselectivity (entry 3). In addition, aromatic lithium and heterocyclic lithium regents provided the desired 1:2 Michael adducts in good yields and good diastereoselectivities (entries 4–9).

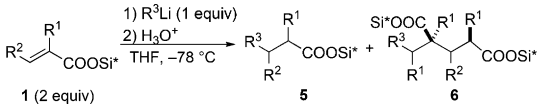
Table 2: Substrate scope of organolithium reagents.[a]



Entry	Product	RLi	Yield [%][b]	d.r.[c]
1	**3b**	EtLi	88	58:42
2	**3c**	BuLi	88	55:45
3	**3d**	^{i}PrLi	83	83:13
4	**3e**	PhLi	91	70:30
5	**3f**	2-MeC_6H_4Li	98	82:18
6	**3g**	2-MeOC_6H_4Li	90	95:5
7	**3h**	1-naphthyllithium	96	85:15
8	**3i**	2-naphthyllithium	99	79:21
9	**3j**	2-pyridyllithium	85	87:13

[a] Reaction conditions: **1a** (0.4 mmol), RLi (0.2 mmol) in THF at −78 °C for 2 h. [b] Yield of the isolated product. [c] d.r. was determined by ^{1}H NMR spectroscopy.

Table 3: Substrate scope of supersilyl α-substituted acrylates.[a]



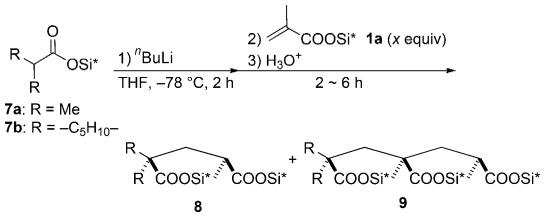
Entry	R^3	**1**	Product	Yield [%][b,c]
1[d]	^{t}Bu	**1b**	**5b**	88
2[d]	^{t}Bu	**1c**	**5c**	86
3[d]	^{t}Bu	**1d**	**5d**	72, d.r. > 99:1
4[e]	^{n}Bu	**1c**	**6c**	94, d.r. 55:45
5[e]	^{t}Bu	**1e**	**6e**	73, d.r. 85:15
6[e]	^{t}Bu	**1f**	**6f**	70
7[e]	^{t}Bu	**1g**	**6g**	68

[a] Reaction conditions: **1** (0.4 mmol), ^{t}BuLi (0.2 mmol) in THF at −78 °C for 2 h. [b] Yield of the isolated product. [c] d.r. was determined by ^{1}H NMR spectroscopy. [d] **5**/**6** = > 99:1. [e] **5**/**6** = 95: < 5.

Next, we turned our attention to the scope of supersilyl α-substituted acrylates (Table 3). Supersilyl α-phenyl acrylate **1b** and supersilyl α-ethyl acrylate **1c** afforded only the 1:1 Michael adduct in good yield, and one equivalent of the starting material was recovered (Table 3, entries 1 and 2). A compound with substituents at the α and β positions underwent a single Michael addition with good yield and excellent diastereoselectivity (entry 3).[11] Compounds with bulky α-substituents only gave a 1:1 Michael adduct. For the reaction of a sterically hindered alkyllithium with **1c**, the 1:2 Michael adduct was obtained in good yield (entry 4). Supersilyl α-fluoro acrylate **1e** gave the 1:2 Michael adduct in good yield with high diastereoselectivity (entry 5), and supersilyl acrylate **1f** gave the product in good yield (entry 6). Reaction of supersilyl 2,4-pentadienoate **1g** with ^{t}BuLi furnished the double 1,6-addition adduct with good yield (entry 7).

Supersilyl isobutyrate **7a** was treated with ^{n}BuLi to form the lithium enolate, followed by the addition of supersilyl methacrylate (Table 4). The use of one equivalent of supersilyl methacrylate **1a** gave virtually a 1:1 Michael adduct in 89% yield and excellent chemoselectivity (entry 1). The use of two equivalents of supersilyl methacrylate **1a** afforded the 1:2 Michael adduct in 60% yield as a single diastereomer together with the 1:1 Michael adduct (8%; entry 2), and the same result was obtained with five equivalents of **1a**, of which 3.3 equivalents was recovered (entry 3). No polymerization occurred when using supersilyl methacrylate. The supersilyl

Table 4: Michael addition **1a** and lithium enolate of ester.[a]



Entry	7	x [equiv]	8/9[b]	Yield [%][c]	d.r.[b]
1	**7a**	1	>99:1	89 (**8a**)	–
2	**7a**	2	12:88	60 (**9a**)	>99:1 (**9a**)
3	**7a**	5	10:90	43 (**9a**)	>99:1 (**9a**)
4	**7b**	1	>99:1	95 (**8b**)	–
5	**7b**	2	22:78	64 (**9b**)	>99:1 (**9b**)

[a] Reaction conditions: 1) **7** (0.2 mmol), ^{n}BuLi (1.05 equiv), THF, −78 °C, 3 h. 2) **1a** (*x* equiv), THF, −78 °C, 2 to 6 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of the isolated product.

cyclohexanecarboxylate **7b** was examined, the use of one equivalent **1a** resulted in the formation of the 1:1 Michael adduct in 95% yield (entry 4). When two equivalents of **1a** was used, the 1:2 Michael adduct was obtained in good yield, good chemoselectivity, and excellent diastereoselectivity (entry 5).

In conclusion, we demonstrated the selective Michael reaction using the bulky "supersilyl" protecting group as an effective carboxyl protection group. This methodology affords the controlled stereoselective formation of either the single and double Michael addition adduct in a single process.

Keywords: chemoselectivity · Michael reaction · protecting groups · supersilyl group · synthetic methods

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[10] For details on the deprotection process and single-crystal X-ray analysis see the Supporting Information. CCDC 1059548 (**4**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[11] The relative configuration of the product **5d** was determined by NOE analysis (see the Supporting Information).

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