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BCSJ Award Article

Lewis Base-Catalyzed Michael Reactions between Trimethylsilyl Enolate and α,β-Unsaturated Carbonyl Compounds

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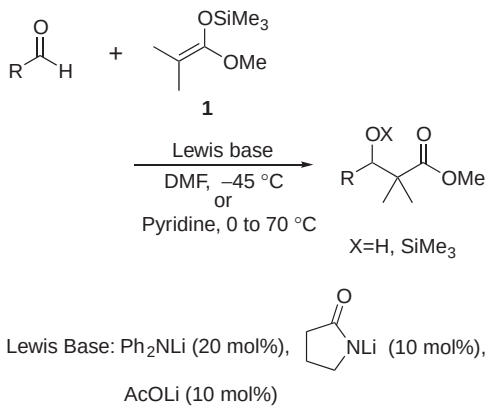
Michael reactions between trimethylsilyl enolates and α,β-unsaturated carbonyl compounds by using a Lewis base catalyst such as lithium benzamide **4** or lithium succinimide **5** in DMF proceeded smoothly to afford the corresponding Michael-adducts in good to high yields (Tables 1–3). In order to extend the scope, Michael reactions catalyzed by lithium acetate (AcOLi), a weak and readily available Lewis base, were studied in detail. AcOLi behaved as an effective Lewis base catalyst in Michael reactions between trimethylsilyl enolates and α,β-unsaturated carbonyl compounds at 0 °C or at room temperature (Tables 4–6). Hindered α,β-unsaturated ketones behaved as excellent Michael-acceptors in the above reaction at room temperature (Table 5). This catalytic Michael reaction also proceeds smoothly in the presence of other lithium carboxylates that are easily prepared in situ by treating carboxylic acids with lithium carbonate (Li_2CO_3) (Scheme 2). This is the first example of Lewis base-catalyzed Michael reactions between α,β-unsaturated carbonyl compounds and trimethylsilyl enolates.

Silyl enolates are stable enolate equivalents and can be isolated by distillation; however, their usefulness in synthetic organic chemistry has not fully been shown because of their weak nucleophilic characters. After crossed aldol reactions between aldehydes and silyl enolates promoted by Lewis acids such as titanium(IV) chloride were reported from our laboratory,[1] silyl enolates are recognized as convenient and useful nucleophiles and have frequently been employed in constructing carbon skeleton. Recently, activation of silyl enolates under neutral or weakly basic conditions was studied intensively: for example, Denmark et al.[2] and Hosomi and co-workers[3] reported reactions using silyl enolates having enhanced Lewis acidic silicon atoms which are reactive toward Lewis bases. Another new method for the activation of silyl enolates was also recently reported from our laboratory: that is, simple and commonly-employed trimethylsilyl (TMS) enolates reacted smoothly with aldehydes to afford the corresponding aldols in the presence of a Lewis base catalyst such as lithium diphenylamide, lithium pyrrolidone or lithium acetate (AcOLi) in *N*,*N*-dimethylformamide (DMF) or pyridine[4] (Scheme 1).



Scheme 1. Lewis base-catalyzed aldol reaction between aldehyde and TMS enolate.

In order to demonstrate the usefulness of the above-mentioned Lewis base catalysts, we further studied the catalytic Michael reaction between TMS enolates and α,β-unsaturated carbonyl compounds. Michael reaction is commonly employed as one of the most important synthetic methods for carbon–carbon bond formation; however, side reactions such as self-condensations of substrates, proton transfers, and concomitant 1,2-additions often take place under basic conditions in conventional Michael reactions.[5] Such undesirable reactions are removed by using silyl enolates as the functional equivalents of Michael donors. This type of reaction has become very popular ever since the Michael reaction between α,β-unsaturated ketones and silyl enolates by the promotion of Lewis acid was reported from our laboratory.[6] Also, several other methods are for the activation of silyl enolates have been reported; for example, fluoride,[7] hydride, or hydroxide[8] ion catalyzed reactions of silyl enolates via the nucleophilic cleavage of the O–Si bond have been shown. Kobayashi et al. reported that the reaction of dimethyl(trifluoromethansulfonyloxy)silyl enol

Published on the web February 11, 2005; DOI 10.1246/bcsj.78.236

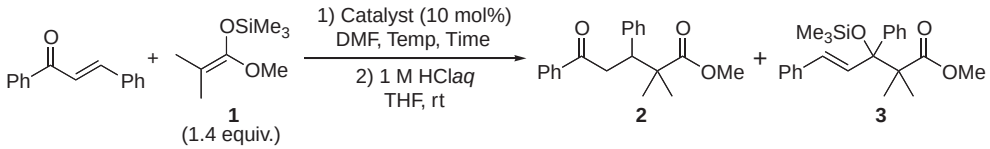
ethers with α,β-unsaturated ketones proceeded smoothly even in the absence of catalysts.[9] In addition, reactions of ketene silyl acetals with α,β-unsaturated carbonyl compounds were shown to take place in DMSO[10] and nitromethane[7c] at room temperature or in acetonitrile at 55 °C[11] and under high pressure in CH_2Cl_2 or acetonitrile.[12] Recently, Hosomi and coworkers reported magnesium chloride-promoted Michael reaction of dimethylsilyl enolates to α-enones.[3b] Some of these methods, however, were shown to have synthetic limitations: i.e., in the case of TMS enolate derived from methyl isobutyrate **1**, the reaction must be carried out at elevated temperatures because of its decreased reactivity.[12] In this paper, we would like to report on a catalytic Michael reaction between TMS enolates and α,β-unsaturated carbonyl compounds by using Lewis base catalysts such as lithium benzamide, lithium succinimide, and lithium acetate (AcOLi).[13]

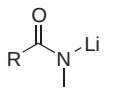
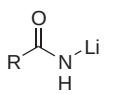
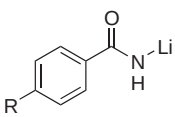
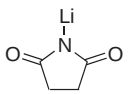
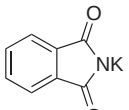
Results and Discussion

Lithium Benzamide or Lithium Succimide-Catalyzed Michael Reactions between Trimethylsilyl Enolate and α,β-Unsaturated Carbonyl Compounds. In the first place, reaction of chalcone and **1** was tried in DMF by using a catalytic amount of lithium diphenylamide or lithium pyrroridone. The Michael-adduct **2** was afforded in 52% or 68% yield, respectively (Table 1, Entries 1 and 2). Then, several lithium amides were screened in order to improve the yield (Table 1). When less hindered amides compared with lithium pyrroridone, such as lithium *N*-methylacetamide or lithium acetamide, were used, the adduct **2** was obtained in high yield together with a small amount of 1,2-addition product, silyl ether **3** (Entries 3 and 5). The amount of **3** decreased when amides having bulky substitutents at R group were used; lithium benzamide turned out to be the most effective Lewis base for the acceleration of the reaction (Entries 6–8). It is interesting to note that lithium succinimide and potassium phthalimide, employed as Lewis base catalysts in Mannich-type reactions,[14] also worked as effective catalysts and the Michael-adduct was obtained in high yield at 0 °C, even though pK_a values of N–H bond of the conjugate acid of the catalyst measured in DMSO were much lower than the values of above-mentioned precursors[15] (Entries 12 and 14). In the absence of the catalyst, on the other hand, the Michael-adduct was not obtained at all, indicating that the above salts behaved as effective Lewis base catalysts in this Michael reaction (Entry 15).

Next, the reactions of TMS enolate **1** with various Michael-acceptors were tried by using lithium benzamide **4** or lithium succinimide **5** as a catalyst (Table 2). Bulky silyl enolate **1** smoothly reacted with various Michael-acceptors to give the corresponding Michael-adducts in high yields at low temperature, except when hinderd α,β-unsaturated ketones were used.

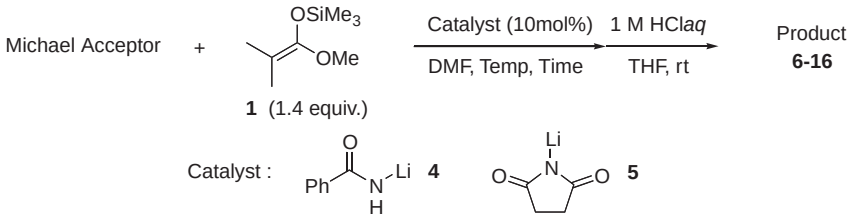
Table 1. Screening of Catalysts for Michael Reaction between Chalcone and TMS Enolate **1**

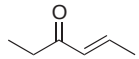
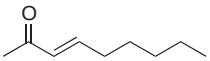
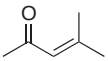
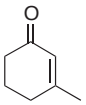
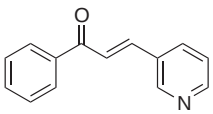
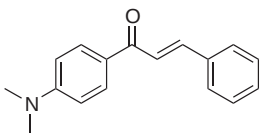


Entry	Catalyst		Temp/°C	Time/h	**2**:**3**	Yield[a]/%
1[b]	Ph_2NLi		–45	3	>99:1	52
2			–45	3	>99:1	68
3		R=Me	–45	2.5	95:5	quant
4		Ph	–45	1.5	98:2	92[c]
5		R=Me	–45	1.5	93:7	97[c]
6		*i*-Pr	–45	1.5	95:5	98[c]
7		*t*-Bu	–45	1.5	97:3	quant[c]
8		Ph	–45	1.5	>99:1	quant
9		R=OMe	–45	1.5	>99:1	95[c]
10		NO_2	–45	1.5	>99:1	95[c]
11			–45	3	>99:1	63
12			0	3	>99:1	90
13			–45→0	3.5	>99:1	73
14			0	1	>99:1	98[c]
15	none		0	1	—	0

a) Total yield of **2** and **3**. Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. b) 20 mol% of catalyst was used. c) Isolated yield.

Table 2. Lewis Base-Catlyzed Michael Reaction between Silyl Enolate **1** and Various Michael Acceptors



Entry	Michael acceptor	Catalyst	Temp/°C	Time/h	Product[a)]	Yield[b)]/%
1	cyclopentenone	**4**	−45	3	**6**	91
2	cyclopentenone	**5**	−45	3	**6**	88
3	cyclohexenone	**4**	−45	3	**7**	94
4	cyclohexenone	**4**	−45	1	**8**	93[c)]
5	methyl vinyl ketone	**4**	−45	3	**9**	90
6		**4**	0	3	**10**	85
7		**4**	−45	3	**11**	42
8		**4**	0	3	**11**	75
9		**4**	rt	3	**11**	40
10		**5**	rt	3	**11**	83
11		**4**	−45 → rt	4	**12**	5
12		**5**	rt	3	**12**	34
13		**4**	−45 → rt	2	**13**	3
14		**5**	rt	6	**13**	44
15		**4**	−45	3	**14**	83
16		**5**	−45	4	**14**	97
17		**4**	0	3	**15**	92
18		**5**	0	3.5	**15**	91
19	methyl acrylate	**4**	−45 → 0	5	**16**	65

All reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). a) See Fig. 1. b) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. c) Reaction was quenched with sat. $NaHCO_3$aq. Isolated yield.

Under the reaction conditions, the silylated Michael-adduct is isolated when the reaction mixture was quenched under basic conditions (Entry 4). In the case of using 3-nonen-2-one as the Michael-acceptor, **5** proved to be a very effective Lewis base catalyst; that is, the reaction proceeded smoothly by using such weakly basic catalyst **5** to afford the corresponding Michael-adduct in high yields. The yield was poor when the same reaction was carried out by using **4** which behaved as a Brønsted base in DMF at room temperature (Entries 9 and 10). From a synthetic point of view, the present Lewis base-catalyzed reaction has a remarkable advantage in forming Michael-adducts, especially when Michael-acceptors having basic functions in the same molecules were used. Expectedly, the above reactions proceeded smoothly to afford the corresponding Michael-adducts in high yields (Entries 15–18).

The present catalytic Michael reaction was further examined by using several other silyl enolates (Table 3). When sterically hindered triethylsilyl enolate derived from methyl isobutyrate was used in place of the above-mentioned TMS enolate **1**, the corresponding Michael-adduct was obtained in only 46% yield (Entry 1). This result indicated that the reaction proceeded via the activation of TMS enolate by forming hypervalent silicates between Lewis bases and the silicon atom of the enolate. Further, the reactivities slightly decreased when TMS enolate derived from methyl propionate were used as a substrate (Entries 2 and 5). The corresponding Michael adducts were obtained in good yields when the reactions were carried out in more concentrated solutions[16] (Entries 3, 4, 6–11).

Lithium Acetate-Catalyzed Michael Reactions between Trimethylsilyl Enolate and α,β-Unsaturated Carbonyl Compounds. A new catalytic Michael reaction between TMS enolates and α,β-unsaturated carbonyl compounds was established under non-acidic conditions by using lithium benzamide **4** or lithium succinimide **5** in DMF, as described in the

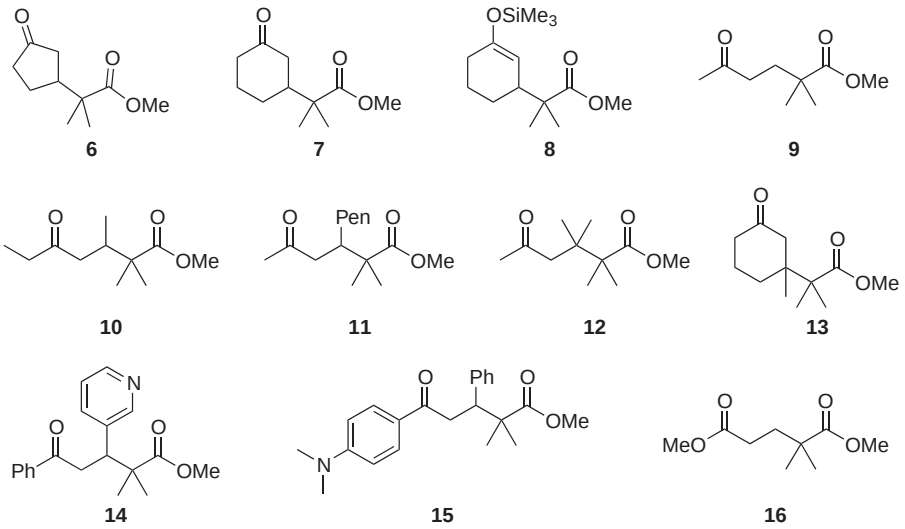
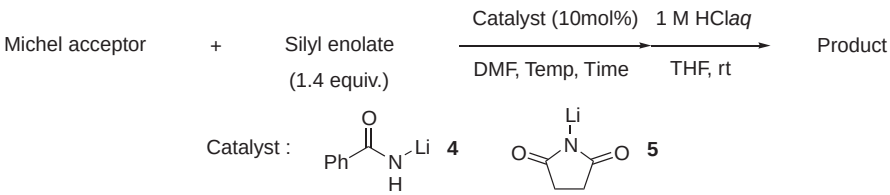
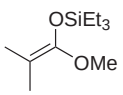
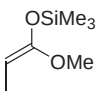
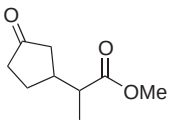
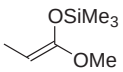
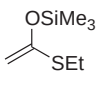
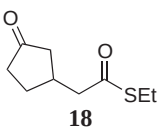
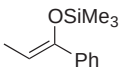
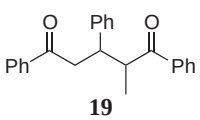
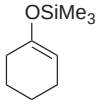
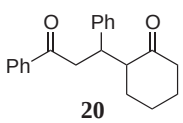


Fig. 1.

Table 3. Lewis Base-Catalyzed Michael Reaction Using Various Silyl Enolates



Entry	Michael acceptor	Silyl enolates	Cat.	Temp /°C	Time /h	Product	Yield[a] /%	*syn*:*anti*[b]
1[c]	cyclopentenone		**4**	−45	3	**6**	46[d]	—
2[c]	cyclopentenone		**4**	−45	1.5	 **17**	71	55:45
3	cyclopentenone		**4**	−45	1		75	52:48
4	cyclopentenone	(*E*:*Z* =5:1)	**5**	−45→0	3.5		40	54:46
5[c]	cyclopentenone		**4**	−45	1.5		63	67:33
6	cyclopentenone		**4**	−45	1		72	64:36
7	cyclopentenone	(*E*:*Z* =1:9)	**5**	−45→0	3		37	63:37
8	cyclopentenone		**4**	−45→0	4	 **18**	66	—
9	cyclopentenone		**5**	−45→0	2		67	—
10	chalcone		**4**	−45	1	 **19**	89	16:84[e]
11	chalcone		**5**	rt	18		62	8:92[e]
12[c]	chalcone		**4**	−20	2	 **20**	quant.[d]	21:79[e,f]
13[c]	chalcone		**5**	70	6		36[d]	35:65[e,f]

Reactions were carried out using Michael acceptor (0.8 mmol) in DMF (3 mL). a) Isolated yield. b) Determined by GC. c) Reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). d) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. e) Determined by ^{1}H NMR analysis (270 MHz). f) Relative configurations were not determined.

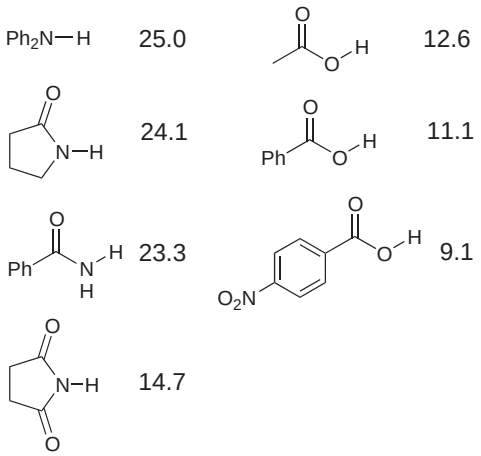


Fig. 2. pK_a values of acidic hydrogens in dimethyl sulfoxide.

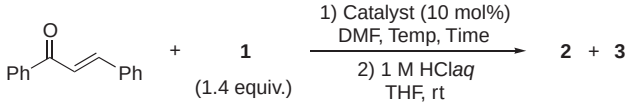
preceding chapter. It is interesting to note that the TMS enolate was activated by the nucleophilic attack of lithium succinimide **5** to its silicon atom although the pK_a value of N–H bond of the succinimide was much lower than that of the benzamide.[15] Next, the use of lithium acetate (AcOLi), a milder and readily-available Lewis base, in place of the above-mentioned lithium salts was examined on the consideration that pK_a values of O–H bonds of the carboxylates are relatively close to that of the N–H bond of succinimide[15] (Fig. 2).

Actually, it was shown that AcOLi-catalyzed aldol reation between TMS enolates and aldehydes proceeded smoothly to afford the corresponding aldols in high yields.[4d–g] The above catalyst, AcOLi, has synthetic advantages such as easy availability, low cost and weak basicity. Also, the acetate can be prepared from AcOH by using weak bases such as lithium carbonate (Li_2CO_3), while preparation of **4** or **5** from amide or imide requires strong bases such as alkyllithium. In addition, from the environmental points of view, lithium acetate is a useful catalyst because of its low toxicity and its disposability without any special treatment.

In the first place, the reaction of chalcone and TMS enolate **1** in DMF was tried by using 10 mol% of AcOLi at −45 °C; the Michael-adduct **2** was obtained in 93% yield together with 1,2-addition product, silyl ether **3**, in 7% yield (Table 4, Entry 1). Next, the reaction conditions were carefully screened in order to reduce the amount of 1,2-adduct (Table 4). The amount of **3** increased when sodium, pottasium, and ammonium were used as counter cations of acetate (Entries 2–4). It was found that the ratio of **2**:**3** increased up to 98:2 when 4-*t*-BuC_6H_4COOLi was used (Entry 11). And the Michael-adduct **2** was obtained in high yield by using AcOLi as a catalyst when the reaction was carried out at 0 °C (Entry 12).[17] In addition, Michael-adduct **2** was also obtained selectively when potassium acetate (AcOK) or lithium isobutyrate was used at 0 °C (Entries 13, 14).

Next, reactions of TMS enolate **1** with various Michael-acceptors were examined by using AcOLi (Table 5). Silyl enolate **1** reacted smoothly with various Michael-acceptors to afford the corresponding Michael-adducts in high yields. The silylated Michael-adduct **8** was isolated by quenching the reaction mixture under basic conditions, similar to the case when lithium benzamide **4** was used (Entry 2). When 3-nonen-2-one was used as Michael-acceptor, AcOLi was more effective than lithium succinimide **5** (Entry 4; compare with Table 2, Entry 10). One of the most characteristic points of the present reaction is that hindered α,β-unsaturated ketones behaved as excellent Michael-acceptors to form the corresponding Michael-adducts in high yields at room temperature, whereas the desired products were obtained only in poor yields when **4** or **5** was used as a catalyst (Entries 5 and 6; compare with Table 2, Entries 11–14). This Lewis base-catalyzed reaction proceeded smoothly when Michael-acceptors having a basic function were used, similar to the case of using **4** or **5** as a catalyst; the corresponding Michael-adduct was afforded in high yield (Entry 6).

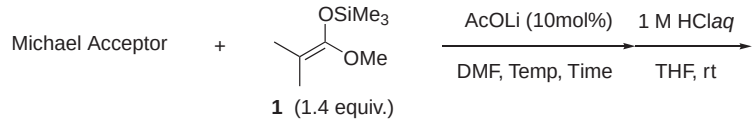
Table 4. Screening of Carboxylate Catalysts for Michael Reaction between Chalcone and TMS Enolate **1**

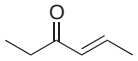
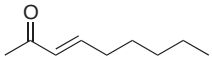
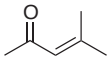
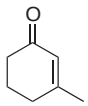
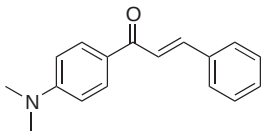


Entry	Catalyst	Temp/°C	Time/h	**2**:**3**	Yield[a]/%
1	AcOLi	−45	1.5	93:7	quant.
2	AcONa	−45	1.5	92:8	quant.
3	AcOK	−45	1	87:13	quant.
4	$AcONMe_4$	−45	1.5	88:12	quant.
5	*i*-PrCOOLi	−45	1.5	93:7	quant.
6	*t*-BuCOOLi	−45	1.5	94:6	98
7	PhCOOLi	−45	1.5	95:5	94[b]
8	4-$MeOC_6H_4$COOLi	−45	1.5	94:6	97[b]
9	4-$NO_2C_6H_4$COOLi	−45	3	97:3	49
10	2,6-$Me_2C_6H_3$COOLi	−45	3	96:4	92[b]
11	4-*t*-BuC_6H_4COOLi	−45	1.5	98:2	94[b]
12	AcOLi	0	0.5	>99:1	quant.
13	AcOK	0	0.5	>99:1	quant.
14	*i*-PrCOOLi	0	0.5	>99:1	quant.

a) Total yield of **2** and **3**. Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. b) Isolated yield.

Table 5. AcOLi-Catalyzed Michael Reaction Using Various Michael Acceptors



Entry	Michael acceptor	Temp/°C	Time/h	Product[a)]	Yield[b)]/%
1	cyclopentenone	0	0.5	**6**	98
2[c)]	cyclopentenone	0	0.5	**8**	quant.
3		0	0.5	**10**	98
4		rt	0.5	**11**	quant.
5		rt	3	**12**	85
6		rt	6	**13**	83
7		0	0.5	**15**	91[d)]
8[e)]	methyl acrylate	rt	6	**16**	64

All reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). a) See Fig. 1. b) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane or 1,3,5-trimethylbenzene (Entry 4) as an internal standard. c) Reaction was quenched with sat. $NaHCO_3$aq. d) Isolated yield. e) 2 equivalents of **1** were used.

The AcOLi-catalyzed Michael reaction was further examined by using several other silyl enolates (Table 6). Several methods were recently reported concerning Lewis base-catalyzed Michael reaction. However, each of them had limitations as to the silyl enolates employed; i.e., one worked only with dimethylsilyl enolates deriveded from ketones,[3b,18] and another performed only with silyl enolates derived from esters.[7c,10,11,19] On the other hand, AcOLi-catalyzed Michael reaction proceeded smoothly to afford the corresponding Michael-adducts in good to high yields even when various TMS enolates derived from esters, thioesters or ketones were used. Moderate diasteroselectivities were shown when silyl enolates derived from *S-t*-butyl propanethioate, propiophenone, or cyclohexanone were used as Michael-donors (Entries 8, 10, 11).

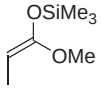
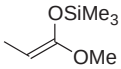
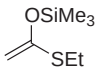
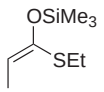
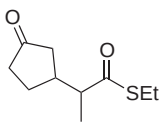
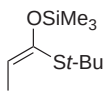
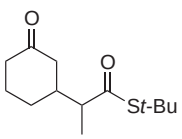
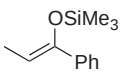
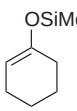
Although the preparation of **4** or **5** is needed to use strong bases such as alkyl lithium, the present catalytic Michael reaction was successfully performed by using various lithium carboxylates that were easily prepared in situ by treating carboxylic acids with lithium carbonate (Li_2CO_3). For example, the Michael reaction of chalcone with silyl enolate **1** gave the Michael-adduct in high yield when 10 mol% of lithium isobutyrate prepared from isobutyric acid and Li_2CO_3 in DMF was used[20] (Scheme 2).

Mechanism of Lewis Base-Catalyzed Michael Reaction between Trimethylsilyl Enolate and α,β-Unsaturated Carbonyl Compounds. The present Lewis base-catalyzed Michael reaction is assumed to proceed by a pathway similar to the pathways for the previously-reported Lewis base-catalyzed aldol reactions[4c] (Scheme 3): that is, it proceeds via a hexacoordinated hypervalent silicate, formed by coordinating a Lewis base and a solvent to the silicon atom of silyl enolates to afford lithium enolate **23**. Subsequent silylation of **23** with the silylated Lewis base afforded *O*-silyl enolate together with the regenerated catalyst. It is generally known that the product-ratio of **23** and lithium aldolate **24**, 1,2-addition product, is dependent on the reaction temperature.[5c] Thus, the desired Michael-adducts were obtained exclusively when the reaction was carried out at 0 °C by using AcOLi as a catalyst (Table 4, Entry 12). Further, the product-ratios of 1,4- vs 1,2-adducts are influenced by the catalyst (Tables 1 and 4). That is, the ratio is controlled by the silylation-step of **24** or **23** with silylated Lewis base formed in the catalytic cycle whose reactivity depended both on their bulkiness and on the electronic effect of their aromatic ring. Since 1,2-addition product **24** has a more hindered structure than 1,4-addition product **23**, silylation of **23** proceeds dominantly with the silylated Lewis bases of mild reactivity.

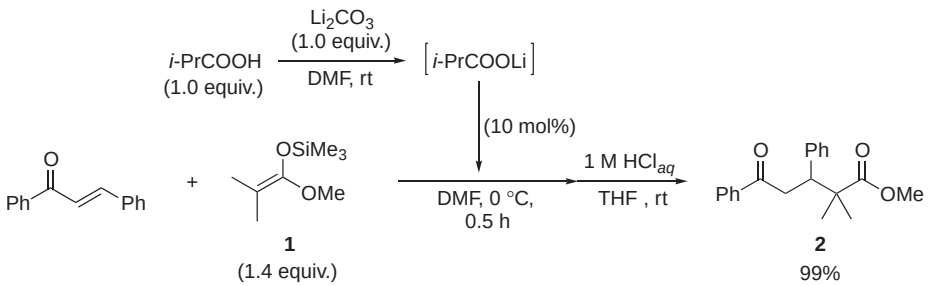
Some silyl enolates afforded the Michael-adducts in better yields when AcOLi was used compared to when **4** or **5** was used (Table 6, Entries 3–5). The reason why yields are lower in the above cases can be assumed: that the deprotonation of Michael-acceptors or -adducts took place easily since these catalysts behaved as a Brønsted base, especially when the reactions were carried out at a higher temperature of 0 °C (Table 3, Entries 4, 7–9). On the other hand, AcOLi, a weak base catalyst, did not cause such an undesirable reaction; therefore, the Michael-adducts were obtained in high yields even at higher temperatures. The reaction is considered to proceed mostly via acyclic transition states, since the silyl enolate de-

Table 6. AcOLi-Catalyzed Michael Reaction Using Various Silyl Enolates

Michel acceptor + Silyl enolate (1.4 equiv.) —AcOLi (10mol%), DMF, Temp, Time→ 1 M HCl*aq*, THF, rt→ Product

Entry	Michel acceptor	Silyl enolates	Temp/°C	Time/h	Product	Yield[a]/%	*syn*:*anti*[b]
1	cyclopentenone		0→rt	3	**17**	64	55:45
2[c]	cyclopentenone	(*E*:*Z* =6:1)	0→rt	3	**17**	74	54:56
3	cyclopentenone		0	2	**17**	89	59:41
4[c]	cyclopentenone	(*E*:*Z* =1:9)	0	1.5	**17**	84	60:40
5	cyclopentenone		0	1	**18**	87	—
6	cyclopentenone		0	1	 **21**	93	59:41
7	cyclohexenone		rt	1	 **22**	84	76:24
8	cyclohexenone		0	2		95	80:20
9	cyclohexenone		−45→−20	3		trace	—
10	chalcone		rt	10	**19**	83[d]	26:74[e]
11	chalcone		70	8	**20**	75[d]	30:70[e,f]

Reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). a) Isolated yield. b) Determined by GC. c) Reactions were carried out using Michael acceptor (0.8 mmol) in DMF (3 mL). d) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. e) Determined by ^{1}H NMR analysis (270 MHz). f) Relative configurations were not determined.

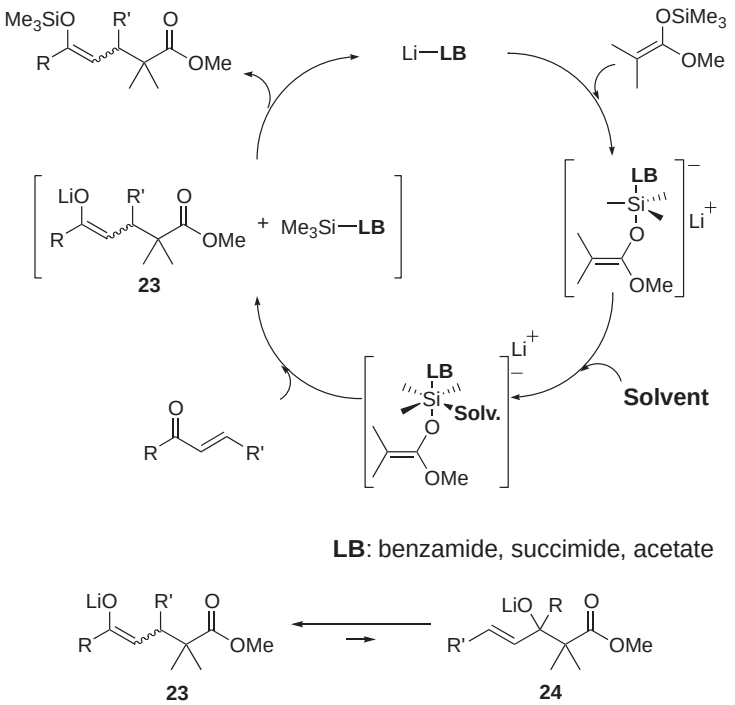


Scheme 2. Michael reaction by using *i*-PrCOOLi prepared from *i*-PrCOOH and Li_2CO_3.

rived from methyl propionate affords the corresponding Michael-adducts with moderate *syn*-diastereoselectivities irrespective of geometries of the two isomeric silyl enolates. In the acyclic transition states, the *syn*-diastereoselectivity of *E*-enolate was lower than that of *Z*-enolate because of steric hindrance between hexacoordinated hypervalent silicate of *E*-enolate and methylene group of cyclepentenone; therefore, *syn*-Michael-adduct is formed more preferentially when *Z*-enolate was used (Fig. 3).

Conclusion

Thus, the Lewis base-catalyzed Michael reactions between TMS enolate and α,β-unsaturated carbonyl compounds under weakly basic conditions in DMF were established. Regarding the effect of catalysts, lithium benzamide **4** or lithium succinimide **5** is effective at −45 °C or at 0 °C and AcOLi, a weak Lewis base catalyst, is also effective at 0 °C or at room temperature.



Scheme 3. Assumed catalytic cycle of Lewis base-catalyzed Michael reaction between TMS enolate and α,β-unsaturated carbonyl compounds.

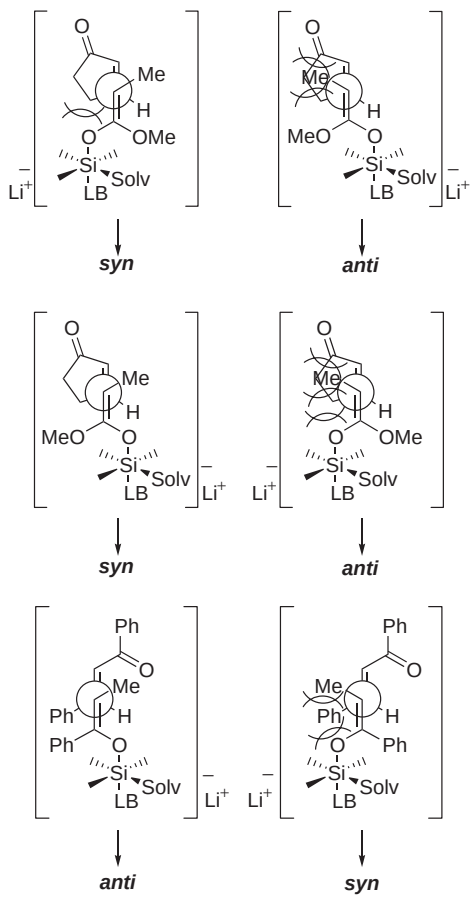


Fig. 3. Acyclic transition state.

This is the first example of a Lewis base-catalyzed Michael reaction using a simple and commonly-used silyl enolate such as TMS enolate. The method is quite practical and is applicable to the synthesis of various 1,5-dicarbonyl compounds, since the reaction smoothly proceeded in the presence of a mild and readily-available Lewis base catalyst.

Experimental

General. All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and are not corrected. Infrared (IR) spectra were recorded on a Perkin Elmer SPECTRUM 1000 or a Horiba FT300 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM EX270L (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on an EX270L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane, with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm; C_6D_6: δ 128.0 ppm). High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX102A or a JEOL MS-700P mass spectrometer. Elemental analyses were conducted using a Yanaco MT-5 CHN Corder. Analytical gas-liquid chromatography (GLC) was performed on a Shimadzu GC-17A instrument equipped with a flame ionizing detector and a capillary column of CBP10 (0.25 mm × 25 m) using helium as carrier gas. Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 GF254, 0.25 mm). Column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. All reactions were carried out under an argon atmosphere in dried glassware. *N*,*N*-Dimethylformamide (DMF)

was dried with P_2O_5 and then distilled from CaH_2 under reduced pressure and dried (molecular sieves, 4A). Lithium acetate and lithium benzoate were purchased from Wako Pure Chemical Industries. Sodium and potassium acetates were purchased from Kokusan Chemical. Tetramethylammonium acetate and potassium phthalimide were purchased from Tokyo Kasei Kogyo. Other Lewis base catalysts were prepared from the corresponding precursors and *n*-BuLi in THF at 0 °C. After the solvent had been removed under reduced pressure, the residue was used without further purification. Lithium isobutyrate was prepared from isobutyric acid and Li_2CO_3 in DMF at room temperature overnight; we used the solution after decantation in the reaction of Scheme 2. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, or Aldrich Chemical. Michael-acceptors were used after purification by distillation or recrystallizaion. Silly enolates and *N*-methylbenzamide were prepared by the usual methods. 4′-(Dimethylamino)chalcone[21] and 1-benzoly-2-(3-pyridyl)ethylene[22] were prepared following literature procedures.

General Procedure for Lewis Base-Catalyzed Michael Reaction between Trimethylsilyl Enolate and α,β-Unsaturated Carbonyl Compound. To a stirred solution of Lewis base (0.04 mmol) in DMF (0.5 mL) were added successively a solution of silyl enolate (0.56 mmol) in DMF (1.0 mL) and a solution of Michael-acceptor (0.4 mmol) in DMF (1.5 mL) at an appropriate temperature. The mixture was stirred for an appropriate time at the same temperature, and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O and the residue was dissolved in a mixture of HCl (1.0 M, 0.5 mL) and THF (5 mL) after evaporation of the solvent. The mixture was stirred for 30 min and then was extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding Michael-adduct. Products and yields are as reported in the text.

Methyl 2,2-Dimethyl-5-oxo-3,5-diphenylpentanoate (2).[19c] White powder; mp 87–88 °C; IR (KBr, cm^{-1}) 1723, 1667, 1256, 1195, 1134, 704, 689; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.21 (s, 3H), 3.26 (dd, $J = 3.5$, 16.7 Hz, 1H), 3.57–3.67 (m, 1H), 3.66 (s, 3H), 3.79 (dd, $J = 3.5$, 10.3 Hz, 1H), 7.17–7.23 (m, 5H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 24.8, 39.9, 46.1, 47.8, 51.9, 126.8, 127.9, 128.0, 128.5, 129.3, 132.9, 137.0, 140.0, 177.7, 198.2; Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%. Found: C, 77.37; H, 7.12%.

Methyl 2,2-Dimethyl-3,5-diphenyl-3-trimethylsiloxypent-4-eonate (3). Colorless oil; IR (neat, cm^{-1}) 2947, 1728, 1458, 1257, 1142, 1065, 887, 841, 756, 702; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.07 (s, 3H), 1.12 (s, 3H), 3.67 (s, 3H), 6.35 (d, $J = 16.5$ Hz, 1H), 7.04–7.43 (m, 11H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 2.1, 21.6, 21.9, 51.6, 52.6, 83.1, 126.6, 126.9, 127.0, 127.8, 128.6, 128.7, 131.8, 134.0, 136.8, 141.1, 176.7; HRMS (FAB+) calcd for $C_{23}H_{29}O_3Si$ $[M - H]^+$ 381.1881, found m/z 381.1883.

Methyl 2-Methyl-2-(3-oxocyclopentyl)propionate (6).[7c,19d,23] Colorless oil; IR (neat, cm^{-1}) 2947, 2885, 1736, 1466, 1404, 1265, 1149; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.22 (s, 3H), 1.57–1.73 (m, 1H), 1.99–2.54 (m, 6H), 3.69 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.4, 22.5, 24.3, 38.7, 40.2, 43.6, 44.8, 51.6, 176.7, 217.7.

Methyl 2-Methyl-2-(3-oxocyclohexyl)propionate (7).[7c,19c,d,23] Colorless oil; IR (neat, cm^{-1}) 2970, 2939, 1720, 1458, 1257, 1196, 1142; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.18 (s, 3H), 1.33–1.46 (m, 1H), 1.53–1.67 (m, 1H), 1.77–1.82 (m, 1H), 1.99–2.40 (m, 6H), 3.68 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.7, 22.0, 25.0, 26.2, 41.1, 43.2, 45.1, 45.7, 51.7, 176.9, 210.8.

Methyl 2-(3-Trimethylsiloxycyclohex-2-enyl)-2-methylpropionate (8).[7c,24] This material obtained by quenching the reaction with saturated aqueous $NaHCO_3$ was purified by column chromatography on silica gel (deactivated by 10 wt % of water, hexane/ethyl acetate = 20/1). Colorless oil; IR (neat, cm^{-1}) 2939, 1728, 1659, 1257, 1188, 1126, 849; ^{1}H NMR (270 MHz, C_6D_6) δ 0.24 (s, 9H), 1.04–1.17 (m, 1H), 1.19 (s, 3H), 1.22 (s, 3H), 1.37–1.68 (m, 3H), 2.00–2.06 (m, 2H), 2.69–2.76 (m, 1H), 3.40 (s, 3H), 4.95 (s, 1H); ^{13}C NMR (68 MHz, C_6D_6) δ 0.4, 21.8, 22.2, 22.8, 24.2, 30.2, 43.2, 45.7, 51.2, 104.9, 152.7, 177.5.

Methyl 2,2-Dimethyl-5-oxohexanoate (9).[19d,23] Colorless oil; IR (neat, cm^{-1}) 2985, 1728, 1142; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.81 (t, $J = 8.1$ Hz, 2H), 2.15 (s, 3H), 2.41 (t, $J = 8.1$ Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.2, 30.0, 33.9, 39.4, 41.5, 51.8, 177.6, 208.0.

Methyl 2,2,3-Trimethyl-5-oxoheptanoate (10). Colorless oil; IR (neat, cm^{-1}) 2978, 2947, 1720, 1458, 1373, 1257, 1188, 1134; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (d, $J = 6.8$ Hz, 3H), 1.05 (t, $J = 7.3$ Hz, 3H), 1.12 (s, 6H), 2.18 (dd, $J = 10.8$, 16.2 Hz, 1H), 2.27–2.55 (m, 4H), 3.67 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 7.7, 15.1, 21.6, 22.4, 35.7, 36.3, 45.2, 45.3, 51.7, 178.0, 210.7; HRMS (EI+) calcd for $C_{11}H_{20}O_3$ $[M]^+$ 200.1407, found m/z 200.1435.

Methyl 2,2-Dimethyl-3-(2-oxopropyl)octanoate (11). Colorless oil; IR (neat, cm^{-1}) 2947, 1728, 1458, 1365, 1257, 1142; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.79 (t, $J = 6.2$ Hz, 3H), 1.03 (s, 3H), 1.04 (s, 3H), 0.91–1.31 (m, 8H), 2.09 (s, 3H), 2.17 (dd, $J = 5.9$, 17.0 Hz, 1H), 2.26–2.34 (m, 1H), 2.45 (dd, $J = 4.3$, 17.0 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.9, 22.1, 22.4, 22.5, 27.7, 30.0, 31.5, 40.1, 45.5, 45.6, 51.6, 178.1, 207.9; HRMS (EI+) calcd for $C_{14}H_{26}O_3$ $[M]^+$ 242.1877, found m/z 242.1871.

Methyl 2,2,3,3-Tetramethyl-5-oxohexanoate (12).[19d] Pale yellow oil; IR (neat, cm^{-1}) 2993, 2947, 1720, 1126; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (s, 6H), 1.15 (s, 6H), 2.15 (s, 3H), 2.49 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.2, 22.2, 33.0, 38.2, 49.0, 49.4, 51.5, 177.0, 208.8.

Methyl 2-Methyl-2-(1-methyl-3-oxocyclohexyl)propionate (13).[19d] Colorless oil; IR (neat, cm^{-1}) 2978, 1713, 1433, 1265, 1146; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.18 (s, 6H), 1.64–1.80 (m, 3H), 1.93–2.02 (m, 1H), 2.14–2.36 (m, 3H), 2.52 (d, $J = 13.5$ Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.2, 20.9 (2C), 21.6, 30.8, 40.7, 42.5, 48.9, 49.0, 51.5, 176.6, 212.0.

Methyl 2,2-Dimethyl-5-oxo-5-phenyl-3-(3-pyridyl)pentanoate (14). White crystals; mp 95–96 °C; IR (KBr, cm^{-1}) 1722, 1669, 1259, 1132; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.23 (s, 3H), 3.32 (dd, $J = 3.5$, 17.0 Hz, 1H), 3.57–3.64 (m, 1H), 3.67 (s, 3H), 3.81 (dd, $J = 3.5$, 10.5 Hz, 1H), 7.19 (ddd, $J = 0.5$, 4.9, 7.8 Hz, 1H), 7.43 (t, $J = 7.3$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 2H), 7.88 (dd, $J = 1.4$, 8.4 Hz, 2H), 8.44 (dd, $J = 1.4$, 4.6 Hz, 1H), 8.48 (d, $J = 1.9$ Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.7, 24.5, 39.3, 45.5, 45.9, 52.0, 122.9, 127.9, 128.6, 133.2, 135.6, 136.5, 136.6, 148.2, 150.6, 177.1, 197.5; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50%. Found: C, 73.19; H, 6.83; N, 4.48%.

Methyl 5-(4-Dimethylaminophenyl)-2,2-dimethyl-5-oxo-3-phenylpentanoate (15). Yellow crystals; mp 161–162 °C; IR (KBr, cm^{-1}) 1721, 1652, 1612, 1238, 1193, 1132; ^{1}H NMR

(270 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.20 (s, 3H), 3.04 (s, 6H), 3.13 (dd, $J = 3.5$, 16.5 Hz, 1H), 3.53 (dd, $J = 1.9$, 16.5 Hz, 1H), 3.65 (s, 3H), 3.80 (dd, $J = 3.8$, 10.3 Hz, 1H), 6.61 (d, $J = 8.9$ Hz, 2H), 7.14–7.22 (m, 5H), 7.82 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.7, 24.7, 38.9, 40.1, 46.2, 48.1, 51.8, 110.6, 125.2, 126.6, 127.8, 129.4, 130.2, 140.4, 153.1, 177.9, 196.1; Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96%. Found: C, 74.57; H, 7.68; N, 3.99%.

Dimethyl 2,2-Dimethylglutarate (16).[25] Colorless oil; IR (neat, cm^{-1}) 2993, 2954, 1736, 1443; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 6H), 1.85–1.91 (m, 2H), 2.26–2.32 (m, 2H), 3.67 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.0, 30.0, 35.1, 41.6, 51.7, 173.9, 177.7.

Methyl 2-(3-Oxocyclopentyl)propionate (17).[7c,11,26] (*Syn*/*anti* = 59/41) Colorless oil; IR (neat, cm^{-1}) 2947, 1736; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 1.23H), 1.22 (s, 1.23H), 1.23 (s, 1.77H), 1.25 (s, 1.77H), 1.51–1.63 (m, 1H), 1.88–2.00 (m, 1H), 2.10–2.43 (m, 6H), 3.69 (s, 1.77H), 3.71 (s, 1.23H); ^{13}C NMR (68 MHz, $CDCl_3$) *Syn* isomer: δ 15.2, 27.2, 38.5, 40.0, 43.4, 44.37, 51.6, 175.6, 217.9, *Anti* isomer (detectable peak): δ 15.8, 27.7, 38.6, 40.2, 42.7, 44.43, 175.5, 217.7; GC ($T_{inj} = T_{det} =$ 200 °C, $T_{col} = 130$ °C) *Syn* isomer: $t_R = 17.6$ min, *Anti* isomer: $t_R = 16.6$ min.

***S*-Ethyl (3-Oxocyclopentyl)thioacetate (18).** Colorless oil; IR (neat, cm^{-1}) 2962, 2939, 1743, 1682; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.6$ Hz, 3H), 1.52–1.73 (m, 1H), 1.90 (dd, $J = 9.2$, 18.1 Hz, 1H), 2.12–2.40 (m, 3H), 2.47 (dd, $J = 5.7$, 17.8 Hz, 1H), 2.57–2.74 (m, 3H), 2.90 (q, $J = 7.6$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.8, 23.5, 29.2, 34.1, 38.3, 44.4, 49.1, 197.7, 217.9; Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58%. Found: C, 57.79; H, 7.73%.

2-Methyl-1,3,5-triphenylpentane-1,5-dione (19).[3b,27] (*Syn*/*anti* = 26/74) Colorless oil; IR (neat, cm^{-1}) 1682, 1450, 972, 756, 702; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (d, $J = 6.8$ Hz, 0.78H), 1.28 (d, $J = 6.5$ Hz, 2.22H), 3.20–3.53 (m, 2H), 3.79–4.00 (m, 2H), 7.09–7.54 (m, 11H), 7.83–7.88 (m, 3.48H), 8.05 (d, $J = 7.3$ Hz, 0.52H); ^{13}C NMR (68 MHz, $CDCl_3$) *Syn* isomer (detectable peak): δ 16.6, 43.5, 44.3, 45.6, 126.8, 128.3, 128.8, 133.2, 136.7, 136.8, 141.4, 198.5, 203.8, *Anti* isomer: δ 14.0, 39.7, 42.7, 45.9, 126.5, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 132.8, 132.9, 136.6, 137.0, 142.8, 198.4, 203.2.

2-(3-Oxo-1,3-diphenylpropyl)cyclohexanone (20).[6b,28] Major isomer: White crystals; mp 149–150 °C; IR (KBr, cm^{-1}) 2920, 1710, 1683, 1449, 747, 698, 570; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.18–1.33 (m, 1H), 1.57–1.77 (m, 4H), 1.96–2.05 (m, 1H), 2.34–2.55 (m, 2H), 2.68–2.77 (m, 1H), 3.17–3.27 (m, 1H), 3.45–3.53 (m, 1H), 3.68–3.77 (m, 1H), 7.13–7.28 (m, 5H), 7.38–7.54 (m, 3H), 7.89–7.92 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.1, 28.5, 32.4, 41.1, 42.3, 44.2, 55.8, 126.6, 128.1, 128.3, 128.4, 132.8, 137.0, 142.0, 198.8, 213.7. Minor isomer: White crystals; mp 134–135 °C; IR (KBr, cm^{-1}) 2925, 1710, 1687, 1449, 1248, 746, 698, 685; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.14–1.21 (m, 1H), 1.48-1.64 (m, 2H), 1.83–2.02 (m, 3H), 2.13–2.35 (m, 2H), 2.60–2.66 (m, 1H), 3.27–3.50 (m, 2H), 3.83–3.90 (m, 1H), 7.05–7.19 (m, 5H), 7.33–7.48 (m, 3H), 7.86–7.90 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.9, 27.6, 29.8, 40.2, 40.3, 42.5, 55.8, 126.3, 128.1, 128.2, 128.4, 132.8, 136.9, 142.5, 198.9, 211.7.

***S*-Ethyl 2-(3-Oxocyclopentyl)propanethioate (21).** (*Syn*/*anti* = 59/41) The diastereomeric ratio was determined by GC compared with an authentic sample prepared by the reported method.[29] Colorless oil; IR (neat, cm^{-1}) 2970, 1743, 1682, 1157, 972; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20–1.29 (m, 6H), 1.50–1.68 (m, 1H), 1.81–2.02 (m, 1H), 2.12–2.61 (m, 6H), 2.83–2.94 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) *Syn* isomer: δ 14.4, 16.7, 23.2, 27.8, 38.6, 40.4, 42.7, 53.5, 202.49, 217.9, *Anti* isomer (detectable peak): δ 15.8, 27.3, 38.4, 40.1, 43.3, 53.6, 202.54, 217.9; GC ($T_{inj} = T_{det} = 200$ °C, $T_{col} = 160$ °C) *Syn* isomer: $t_R = 18.0$ min, *Anti* isomer: $t_R = 19.1$ min; HRMS (FAB+) calcd for $C_{10}H_{17}O_2S$ $[M + H]^+$ 201.0944, found m/z 201.0975.

***S-t*-Butyl 2-(3-Oxocyclohexyl)propanethioate (22).**[30] (*Syn*/*anti* = 80/20) The diastereomeric ratio was determined by GC compared with the authentic sample prepared by the reported method.[29] Colorless oil; IR (neat, cm^{-1}) 2954, 1713, 1682, 957; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12 (d, $J = 6.8$ Hz, 2.4H), 1.16 (d, $J = 7.0$ Hz, 0.6H), 1.46 and 1.47 (2s, 9H), 1.38–2.48 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) *Syn* isomer: δ 14.7, 24.9, 29.2, 29.7, 41.3, 41.7, 44.9, 48.1, 53.7, 203.3, 210.8, *Anti* isomer (detectable peak): δ 14.9, 24.8, 28.1, 41.1, 41.6, 45.8, 53.5, 203.1, 210.7; GC ($T_{inj} = T_{det} = 200$ °C, $T_{col} = 160$ °C) *Syn* isomer: $t_R =$ 16.5 min, *Anti* isomer: $t_R = 17.4$ min; Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15. Found: C, 64.13; H, 9.41.

This study was supported in part by a Grant of the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology (MEXT).

The authors wish to thank Dr. Hironori Tsutsui, Mr. Masakazu Nagasawa, and Mrs. Tomoko Shinohara, Otsuka Pharmaceutical Company, for their kind help with IR, high resolution mass spectrometry, and elemental analyses.

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17 The Michael-adduct **2** was not obtained at all by treating silyl ether **3** with the reaction conditions [AcOLi (10 mol%), DMF, 30 min].

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