

Catalytic Asymmetric Michael Reaction of Methyl Alkynyl Ketone Catalyzed by Diphenylprolinol Silyl Ether

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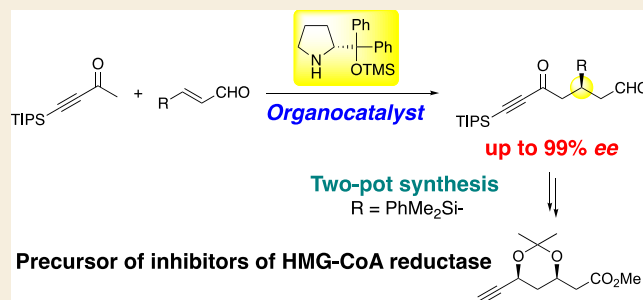
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ABSTRACT: The asymmetric Michael reaction of methyl alkynyl ketone and α,β -unsaturated aldehyde catalyzed by diphenylprolinol silyl ether was developed. Although methyl alkynyl ketone is a good Michael acceptor, it also acts as a Michael donor to afford the synthetically important δ -oxo aldehydes with excellent enantioselectivity. The products possessing several functional groups, such as alkyne, ketone, and aldehyde moieties, are useful chiral building blocks for further synthesis. Using this reaction as a key step, a side chain of atorvastatin (Lipitor), an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, was synthesized in a two-pot sequence with excellent diastereo- and enantioselectivities.

KEYWORDS: organocatalyst, Michael reaction, diphenylprolinol silyl ether, iminium ion, Lipitor, methyl alkynyl ketone, HMG-CoA reductase



Alkynyl ketones (conjugated ynones) are versatile building blocks in synthetic organic chemistry^{1,2} because, in addition to acting as good Michael acceptors, the ketone moiety can be converted into several functional groups. Moreover, the alkynyl moiety can be utilized in metal-mediated [2 + 2] cycloadditions,³ reductive coupling reactions,⁴ and alkyne–alkene and alkene–alkyne coupling reactions.⁵ For the derivatization of alkynyl ketones, the addition reaction of alkynyl ketones is a useful method. In the case of asymmetric catalytic addition reactions of alkynyl ketones as a nucleophile, Trost^{6,7} and Shibasaki⁸ reported the use of chiral Zn^{9,10} and a Lewis acid–Brønsted base two-center catalyst,¹¹ respectively, to promote aldol reactions. Trost also reported the Mannich reaction of alkynyl ketones using the same chiral catalyst and demonstrated the synthetic utility of an alkynyl ketone moiety.^{12,13}

On the other hand, the Michael reaction is an important carbon–carbon bond-forming reaction.^{14–16} However, an asymmetric catalytic Michael reaction of alkynyl ketones as a Michael donor has been regarded as a difficult reaction because it also acts as a good Michael acceptor. To our knowledge, there are no reports on the asymmetric metal-catalyzed reaction with alkynyl ketones as a nucleophile.

The field of organocatalysis has developed very rapidly^{17,18} and many organocatalyst-mediated Michael reactions have been reported.¹⁹ Even in the field of organocatalysis, the direct use of alkynyl ketone as a Michael donor is difficult. Ramachary reported the reaction of methyl alkynyl ketone with α,α -doubly activated alkene to afford a domino Michael/Michael product without isolation of a Michael product (eq

1).^{20–22} Instead of methyl alkynyl ketones, activated methyl alkynyl ketones such as alkoxycarbonyl, aryl, vinyl, or alkoxy-substituted methyl alkynyl ketones^{23–25} are reported to react with nitroalkene, catalyzed by bifunctional Brønsted base/H-bond catalyst, to afford the Michael products with excellent enantioselectivity (eq 2 and 3). There are no reports of the asymmetric Michael reaction of methyl alkynyl ketone itself as a nucleophile, even in the field of organocatalysis.

Recently, we described a diphenylprolinol silyl ether^{26,27}-mediated Michael reaction of ketone,²⁸ in which an enolate is a reactive species.²⁹ We thought that methyl alkynyl ketones would act as good Michael donors to generate the corresponding enolate in the presence of diphenylprolinol silyl ether to react with α,β -unsaturated aldehyde to afford synthetically useful δ -oxo aldehydes (eq 4). Here, we describe the first asymmetric catalytic Michael reaction of methyl alkynyl ketones and its application to the pot-economical synthesis of a key intermediate of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.

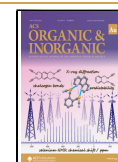
First, we examined the reaction of 4-(*p*-nitrophenyl)-but-3-yn-2-one and cinnamaldehyde, catalyzed by diphenylprolinol silyl ether. Although we investigated the reaction under several

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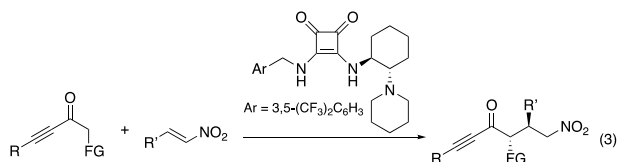
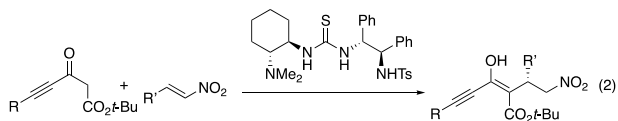
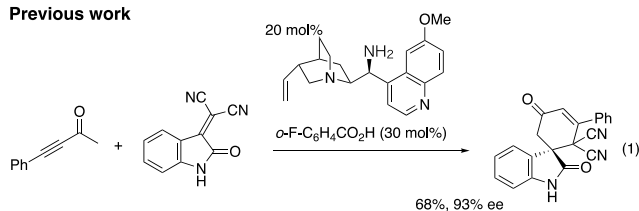
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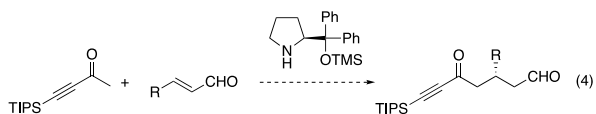


Previous work



FG = aryl, vinyl, alkoxy

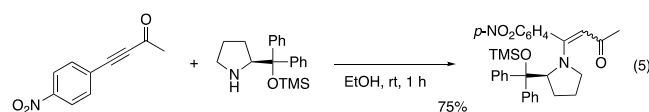
Present work



reaction conditions, the starting aldehyde remained unchanged in most cases. When an equimolar amount of alkyne ketone and a catalyst was used, the Michael adduct of the catalyst and alkyne ketone was isolated (eq 5). This result indicates that alkyne ketone is a good Michael acceptor, which reacts with

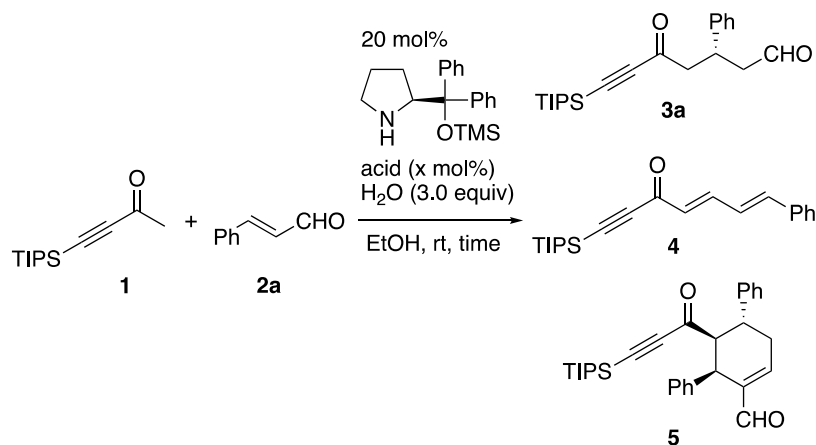
the amine catalyst. With an expectation that the bulky substituent at the 4-position of but-3-en-2-one would suppress this Michael reaction, we examined the reaction of 4-triisopropylsilyl-but-3-en-2-one (**1**) in the presence of several acids (Table 1). Using strong acids such as trifluoroacetic acid, the reaction did not proceed (entry 1). The desired product **3a** was isolated in a 10% yield when benzoic acid was employed, and two side products, **4** and **5**, were also obtained (entry 2). Compound **4** was an aldol (1,2-addition) condensation product, whereas **5** was derived from the double Michael reaction of **1** and two molecules of **2a**, followed by intramolecular aldol condensation. Better yields were obtained when acetic acid and pivalic acid were used (entries 3 and 4). In the case of *p*-nitrophenol, the amount of acid was important. In the presence of 100 mol % *p*-nitrophenol, the desired product **3a** was obtained in a 22% yield, along with the side product **5** (entry 7); in the presence of 10 mol % *p*-nitrophenol, however, **3a** was obtained in the highest yield (69%) with excellent enantioselectivity (entry 5).

The reaction mechanism would be similar to that of the Michael reaction of cyclohexanone:²⁹ An iminium ion, which was generated from **2a** and diphenylprolinol silyl ether, would react with an enolate of methyl ketone **1** to afford Michael product **3a**.



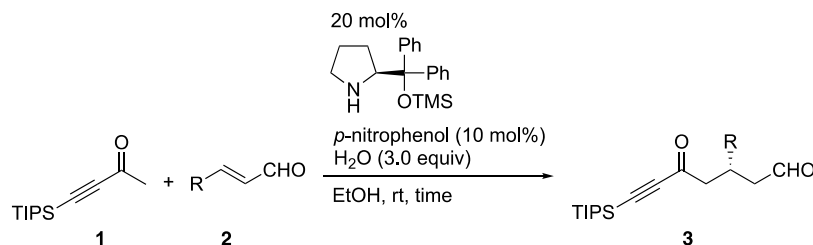
Having established the best reaction conditions, the generality of the reaction was then investigated (Table 2).

Table 1. Effects of Acids and Their Amounts in the Michael Reaction of **1** and **2a**^a



entry	acid (<i>x</i> mol %)	time (h)	yield (%) ^b		
			3a	4	5
1	CF ₃ CO ₂ H (10)	24	0	0	0
2	PhCO ₂ H (10)	12	10	15	20
3	CH ₃ CO ₂ H (10)	8	23	11	15
4	<i>t</i> -BuCO ₂ H (10)	7	39	10	9
5	<i>p</i> -nitrophenol (10)	3	69 ^c	0	0
6	<i>p</i> -nitrophenol (50)	2.5	42	8	8
7	<i>p</i> -nitrophenol (100)	2	22	13	18

^aUnless otherwise shown, reactions were performed by employing cinnamaldehyde **2a** (0.18 mmol), ketone **1** (0.15 mmol), organocatalyst (0.030 mmol), water (0.45 mmol), and acid (indicated amount) in EtOH (0.60 mL) at room temperature for the indicated time. ^bIsolated yield. ^cEnantiomeric excess is 95%.

Table 2. Generality of the Michael Reaction of 1 and 2^a

entry	R	time (h)	yield ^b (%)	ee ^c (%)
1	Phenyl (2a)	3	69	95
2	<i>p</i> -MeO-C ₆ H ₄ (2b)	24	50	95
3	<i>p</i> -Br-C ₆ H ₄ (2c)	2	71	94
4	<i>m</i> -Br-C ₆ H ₄ (2d)	2	75	95
5	<i>o</i> -Br-C ₆ H ₄ (2e)	2	78	95
6	2-furyl (2f)	30	76	94
7	SiMe ₂ Ph (2g)	12	69	98
8	Me (2h)	24	55	76

^aReactions were performed by employing α,β -unsaturated aldehyde 2 (0.18 mmol), ketone 1 (0.15 mmol), organocatalyst (0.030 mmol), water (0.45 mmol), and *p*-nitrophenol (0.015 mmol) in EtOH (0.60 mL) at room temperature for the indicated time. ^bIsolated yield. ^cEnantiomeric excess (ee) of the products, as determined by HPLC analysis over a chiral solid phase after conversion to α,β -unsaturated ester by the treatment with Ph₃P = CHCO₂Et.

Substrates with electron-rich aryl groups such as *p*-methoxyphenyl at the 3-position of propenal were suitable, affording good yield and excellent enantioselectivity, although the reaction was slow (entry 2). Electron-deficient aryl groups such as *p*-bromo, *m*-bromo-, and *o*-bromo phenyls were also suitable substituents, and the reaction was completed within 2 h in good yield with excellent enantioselectivity (entries 3–5). Heteroaromatics such as furyl afforded good results (entry 6), as did silyl-substituted propenal. In the latter case, the C–Si bond could be converted into the corresponding C–OH bond (see below)^{30,31} to provide the Michael product with 98% ee (entry 7). The Michael reaction also proceeded in the case of crotonaldehyde, for which moderate enantioselectivity was obtained (76% ee, entry 8).

Inhibitors of HMG-CoA reductase are important medicines,^{32,33} and several synthetic statins such as atorvastatin (Lipitor),^{34–36} rosuvastatin,³⁷ and fluvastatin³⁸ are commonly used (Figure 1). The key common unit in the side chain of

these statins is β,δ -*syn*-dihydroxy carboxylic acid, and a useful synthetic intermediate of these medicines is protected δ -alkynyl β,δ -*syn*-dihydroxy ester 6.^{39,40}

One-pot operations are an effective method for carrying out several transformations and forming several bonds in a single pot, while simultaneously eliminating several purification steps, minimizing chemical waste generation, and saving time.^{41–43} Based on this concept, we examined the pot-economical synthesis of 6 (Scheme 1).

The first pot reaction started from the asymmetric Michael reaction of 1 and silylated propenal 2g using an (*R*)-diphenylprolinol silyl ether catalyst. After the removal of the solvent under reduced pressure and addition of *t*-BuOH and water in the same reaction vessel, the Michael adduct *ent*-3g was converted into carboxylic acid 7 by Pinnick–Kraus oxidation.^{44,45} Remaining oxidants were reduced upon the addition of acetaldehyde,^{46,47} which was converted into acetic acid. Generated acetic acid and excess acetaldehyde were removed under reduced pressure. The treatment of 7 with TMSCHN₂ afforded methyl ester 8, which was reduced with NaBH₄ to afford *syn* alcohol 9 as a single isomer with excellent diastereoselectivity (see below). Acetic acid was added, which reacted with the remaining NaBH₄, and the solvent was changed from MeOH to CH₂Cl₂. Addition of CSA in the same reaction vessel promoted the lactonization to afford lactone 10, which was purified and isolated in a 42% yield from the first Michael reaction. Five reaction steps, (1) Michael reaction, (2) oxidation, (3) esterification, (4) reduction, and (5) lactonization, were conducted in a single reaction vessel. It should be noted that the one-pot reaction proceeds efficiently by suitable quenching of the reagents in situ,⁴² even though both oxidation and reduction steps are involved.

The second pot sequence started with the removal of the TIPS group from 10 by the addition of *n*-Bu₄NF (TBAF) to afford 11. After neutralization of the reaction mixture by the addition of acetic acid, the addition of HBF₄·OEt₂ and MgSO₄ converted the Si–Ph bond into a Si–F bond,^{30,31} in which MgSO₄ suppressed the side reaction of alkyne and water. After neutralization of the reaction mixture with *n*-Bu₄NOH,

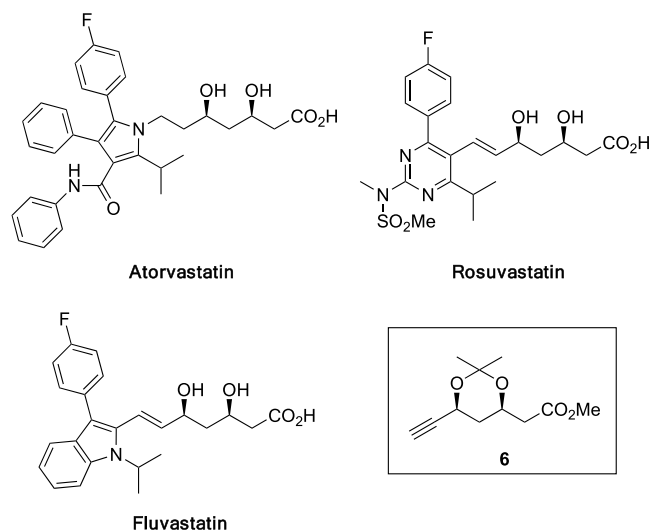
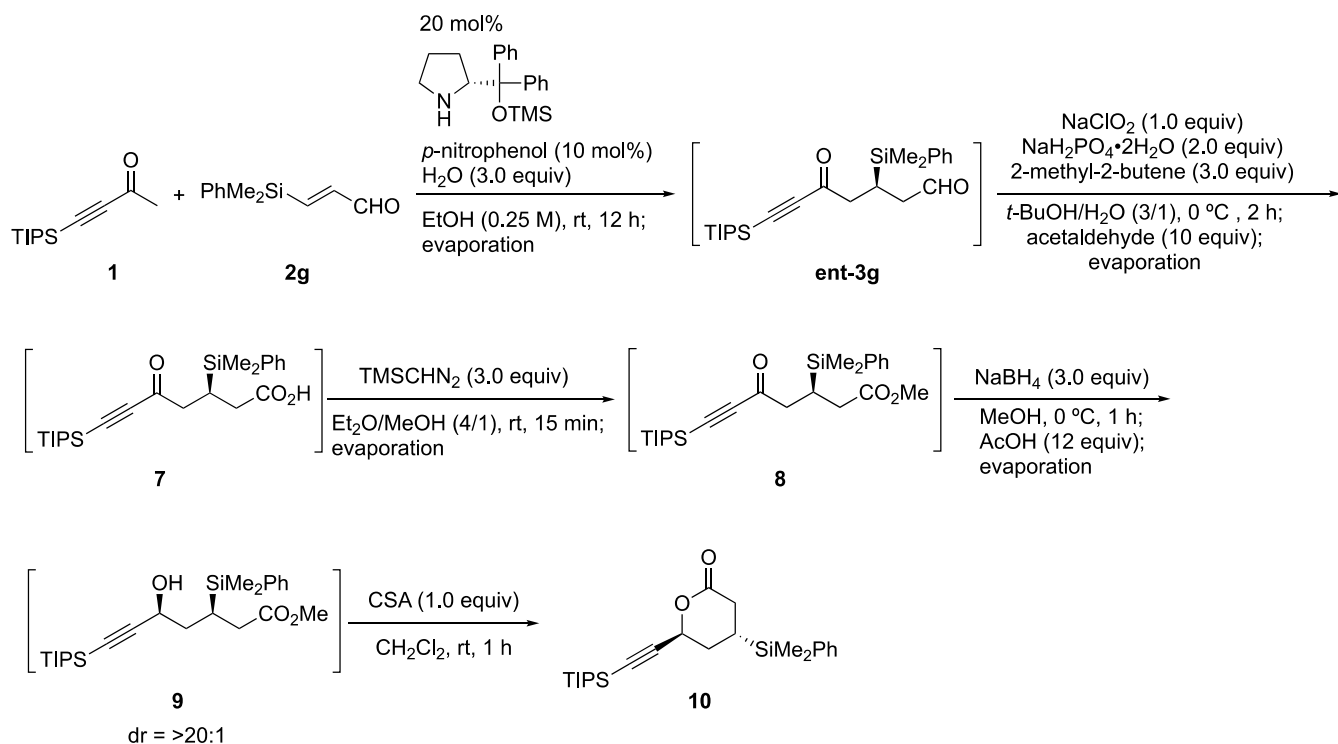
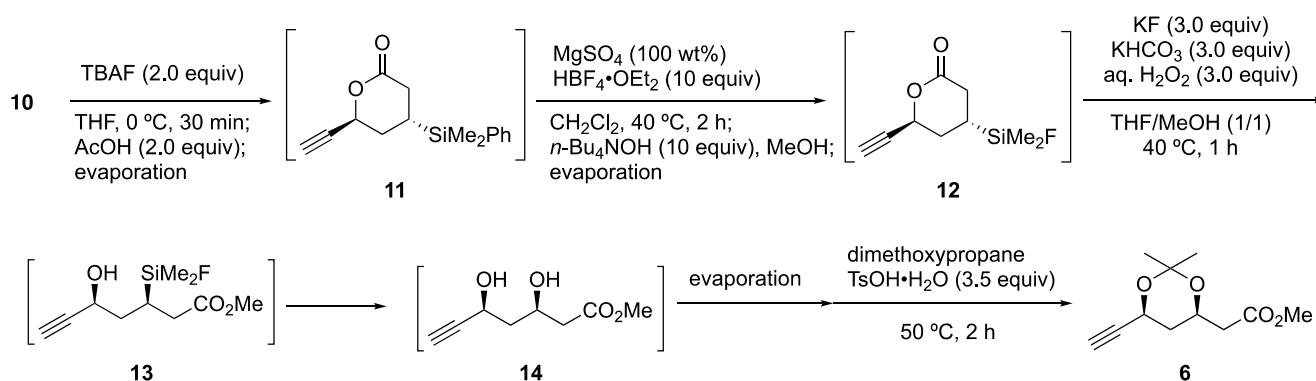


Figure 1. Synthetic statins and key intermediate 6.

Scheme 1. Two-pot Synthesis of Key Intermediate 6 of Inhibitors of HMG-CoA Reductase



Five reaction steps in one-pot sequence, Yield 42%



Five reaction steps in one-pot sequence, Yield 40%

Total two pots, Total yield 16%

addition of H₂O₂, KF, and KHCO₃ in a mixed solvent of THF and MeOH^{30,31} afforded the dihydroxy methyl ester **14** by opening lactone to hydroxy ester **13**, followed by oxidative conversion of the C–Si bond into the C–OH bond. Protection of diol moiety **14** with dimethoxypropane gave acetal **6**. The latter was obtained in a 40% yield from lactone **10** in a single reaction vessel. Five reaction steps, (1) the removal of the TIPS group, (2) conversion of the Si–Ph bond into a Si–F bond, (3) conversion of the C–Si bond into a C–OH bond, (4) opening of lactone to hydroxy ester, and (5) acetal protection of 1,3-diol, were conducted in a single reaction vessel.

It should be mentioned that the position of the Tamao–Fleming reaction in the sequence is important. The Tamao–

Fleming reaction was successful from **11** to **14**, but it did not proceed well for compounds **8** and **9**.

The useful key intermediate **6** was prepared from the Michael reaction using only two reaction vessels with a total yield of 16%. This is a highly diastereo- and enantioselective synthesis. Compound **6** was further transformed into vinyl derivative **15**,^{39,40,48} which is also a useful chiral building block for the synthesis of inhibitors of HMG-CoA reductase (eq 6).

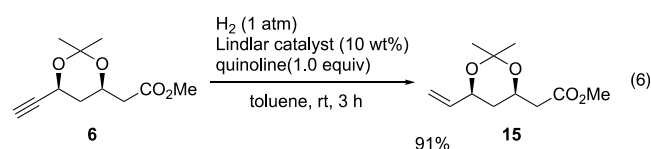
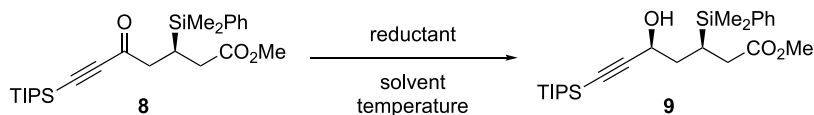
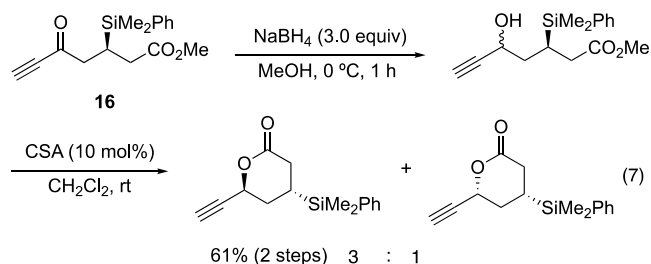


Table 3. Effect of Reducing Reagents in the Reduction of **8**^a

entry	reductant	solvent	temp (°C)	yield (%) ^b	syn:anti
1	(-)-DIP-Cl ^c	THF	-20	62	>20:1
2	L-selectride	THF	-78	58	>20:1
3	BH ₃ ·(<i>t</i> -BuNH ₂)	CH ₂ Cl ₂	0	81	1:1
4	NaBH ₄ ^d	MeOH	0	88	>20:1

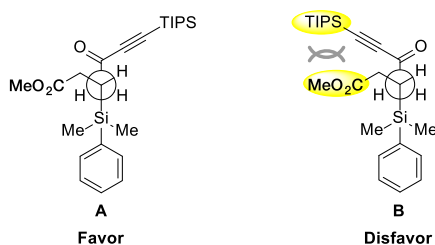
^aUnless otherwise shown, reactions were performed by employing ketone **8** (0.10 mmol) and reductant (0.10 mmol) in the indicated solvent (0.30 mL) at the indicated temperature. ^bIsolated yield. ^cAmount of the reductant is 0.20 mmol. ^dAmount of the reductant is 0.30 mmol.

The diastereoselectivity of the reduction of **8** was notable. When the diastereoselective nucleophilic addition of β -silyl-substituted ketone was systematically investigated by Fleming,⁴⁹ moderate selectivity was obtained in most cases. In the present reduction, excellent diastereoselectivity was observed, which is very rare. We investigated the use of several reducing reagents with isolated **8** (Table 3). Chiral reducing reagents such as (-)-*B*-chlorodisopinocampheylborane ((-)-DIP-Cl)^{50,51} gave excellent diastereoselectivity. Bulky reducing reagents such as L-selectride also gave excellent selectivity. On the other hand, a 1:1 mixture was obtained in the case of BH₃·(*t*-BuNH₂). When NaBH₄ was employed in MeOH, both an excellent yield and diastereoselectivity were observed; however, for similar substrate **16**, without a TIPS moiety, low diastereoselectivity was observed (the relative configuration was determined after conversion into the corresponding lactone; eq 7). Thus, the use of a TIPS protecting group for



the alkyne is essential for the high selectivity, even though it is far from the reacting carbonyl group. This selectivity would be explained by the Felkin–Anh model, as proposed by Fleming in a similar system (Figure 2). The bulky PhMe₂Si and alkynyl ketone adopt an antiperiplanar conformation. As conformer B is unfavorable because of the repulsion caused by the bulky TIPS group, the reaction would proceed from conformer A to afford the excellent diastereoselectivity observed.

In summary, we developed the first asymmetric Michael reaction of methyl alkynyl ketone and α,β -unsaturated

Figure 2. Stable conformation of **8**.

aldehyde, which was catalyzed by diphenylprolinol silyl ether to afford the synthetically important δ -oxo aldehydes bearing an alkyne moiety, with excellent enantioselectivity. Although 4-triisopropylsilyl-but-3-yn-2-one was the only methyl alkynyl ketone used in the present study,⁵² the silyl substituent can be converted into many substituents and functional groups. Because the products possess several functional groups such as alkyne, ketone, and aldehyde moieties, and are generated with excellent enantioselectivity, they would be useful chiral building intermediates. The synthetic utility of the alkynyl ketone moiety has already been well established by Trost's group.^{12,13} By the application of this Michael reaction, chiral building block **6** of the inhibitors of HMG-CoA reductase can be synthesized in two pots with excellent diastereo- and enantioselectivities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00054>.

Experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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