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COMMUNICATION

Asymmetric domino Mukaiyama Michael/Michael reaction catalyzed by diphenylprolinol silyl ether

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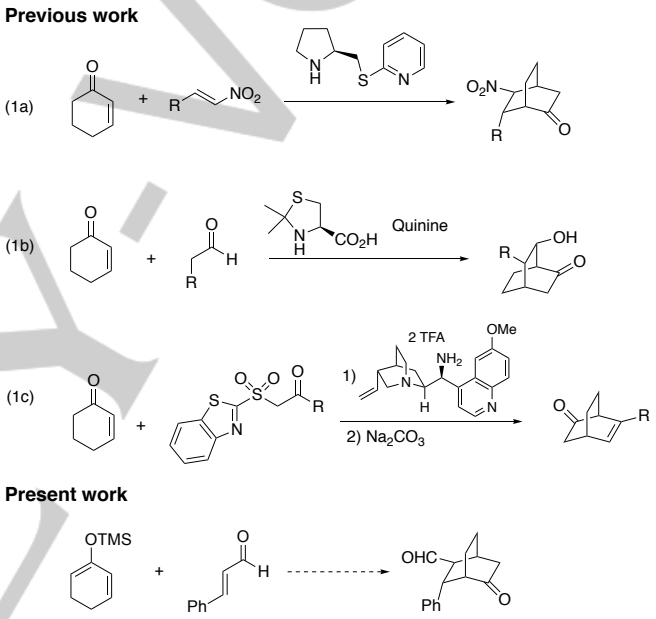
Abstract: The asymmetric catalytic Mukaiyama Michael reaction between α,β-unsaturated aldehydes and silyl enol ether derived from a cyclic ketone was catalyzed by diphenylprolinol silyl ether to afford Michael products with excellent diastereo- and enantioselectivities. Bicyclo[2.2.2]octanone derivatives can be synthesized as a single isomer in a nearly optically pure form via a two-step, one-pot reaction, comprising the sequential Mukaiyama Michael reaction and intramolecular Michael reaction starting from dienol silyl ether and α,β-unsaturated aldehydes, catalyzed by diphenylprolinol silyl ether. In the second Michael reaction, positive kinetic resolution occurred to increase the enantioselectivity.

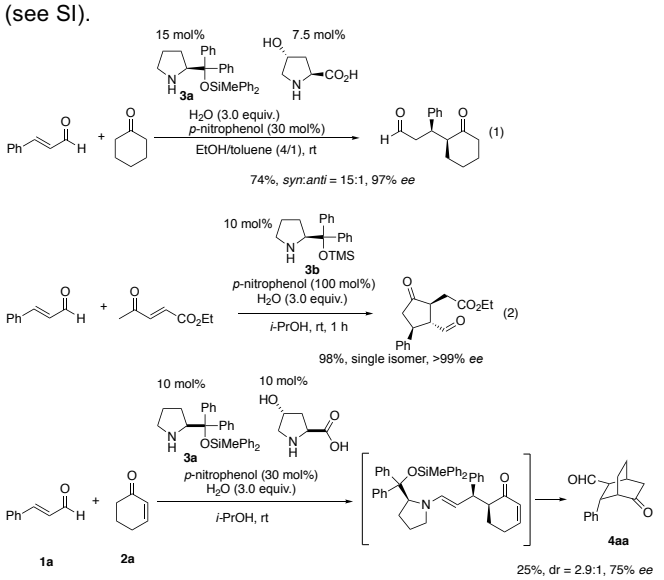
The bicyclo[2.2.2]octane structure has been found in several natural products,[1] and its efficient synthesis is one of the important topics in synthetic organic chemistry. Recently, organocatalysts[2] have been successfully employed for the synthesis of a chiral bicyclo[2.2.2]octane moiety.[3] The [4+2] cycloaddition reaction is one of the most straightforward methods for the synthesis of bicyclo[2.2.2]octane derivatives, and there are a couple of examples using cyclohexenone as a four-carbon component. The asymmetric Diels–Alder reaction of cyclohex-2-enone and nitroalkene was catalyzed by a chiral diamine, in which an amino diene is an intermediate (Scheme 1, 1a).[4] Domino Michael/intramolecular aldol reaction of aldehyde and cyclohex-2-enone was catalyzed by the combined use of quinine and secondary amine to afford bicyclo[2.2.2]octanone with good enantioselectivity (1b).[5] Domino Michael/aldol/Smiles rearrangement was catalyzed by an organocatalyst derived from cinchona alkaloid (1c).[6] Although there are several excellent methods,[3] there is no asymmetric catalytic reaction using silyl dienol ether of a cyclohex-2-enone and α,β-unsaturated aldehyde for the formation of bicyclo[2.2.2]octanone derivative, which is a formal Diels–Alder reaction, even including the metal catalyst and Lewis acid catalyst. In this paper, we describe the first asymmetric one-pot Michael/Michael reaction for the formation of chiral bicyclo[2.2.2]octanone derivatives from silyl dienol ether of cyclohex-2-enone and α,β-unsaturated aldehyde with excellent diastereo- and enantioselectivities.

Recently, we reported the asymmetric Michael reaction of cyclohexanone and α,β-unsaturated aldehyde catalyzed by the combined use of diphenylprolinol silyl ether[7] and secondary amine (Eq. 1),[8] and asymmetric domino Michael/Michael reaction of α,β-unsaturated aldehyde and ethyl 4-oxopent-2-enoate to afford trisubstituted cyclopentanone derivatives (Eq. 2).[9] As an extension of this reaction, we expected a following domino Michael/Michael reaction. When we employ cyclohex-2-enone **2a** instead of cyclohexanone, the Michael reaction of α,β-unsaturated aldehyde as a Michael acceptor would proceed to afford an enamine, from which the second intramolecular Michael reaction would proceed to provide a bicyclo[2.2.2]octanone derivative **4aa** (Scheme 2). When we treated cinnamaldehyde **1a** and cyclohex-2-enone **2a** in the presence of diphenylprolinol silyl ether **3a**, 4-hydroxyproline, *p*-nitrophenol, and water, which is the best condition for the Michael reaction of cyclohexanone and α,β-unsaturated aldehyde, the reaction proceeded to provide the bicyclo[2.2.2]octanone derivative **4aa** in low yield (25%) with low diastereoselectivity (2.9:1) with moderate enantioselectivity (75% *ee*). To improve the yield and selectivity, the reaction conditions including the two amine catalysts, acid additive, and solvent were



Scheme 1. The synthesis of chiral bicyclo[2.2.2]octanone derivatives from cyclohex-2-enone or its silyl enol ether derivative

investigated in detail, but we could not obtain satisfactory results (see SI).



Scheme 2. Domino Michael/Michael reaction for the synthesis of bicyclo[2.2.2]octanone derivative **4aa**

Next, we decided to examine the Mukaiyama Michael[10]/Michael reaction using silyl dienol ether **5a** (Figure 1) instead of using cyclohex-2-enone **2a**. Before the investigation of silyl dienol ether **5a**, we checked the Mukaiyama Michael reaction of silyl enol ether **6a** catalyzed by organocatalyst. Although it is known that the Mukaiyama Michael reaction of silyl enol ether with α,β-unsaturated aldehyde is catalyzed by organocatalysts, the reported reactions are limited to the silyl enol ether of aryl methyl ketone[11] and S-alkyl and 1-pyrrolyl silyl ketene acetals,[12] while siloxyfuran[13] and 2-siloxypyrrole derivative,[14] and dienol silyl ether[15] were employed in the vinylogous Mukaiyama Michael reaction. There is no report of the organocatalyst-mediated Mukaiyama Michael reaction of silyl enol ether **6a** of nonactivated carbonyl compounds such as cyclohexanone, as far as we were aware. Before the investigation of the reaction of silyl dienol ether **5a**, the Mukaiyama Michael reaction of silyl enol ether **6a** using organocatalyst was investigated.

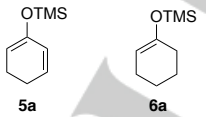
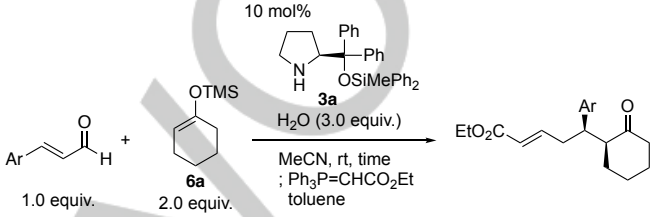


Figure 1. Silyl dienol ether **5a** and silyl enol ether **6a** used in this study

After the optimization of reaction conditions (Table S1), we could obtain good results using diphenylmethylsilyl ether **3a**[16] in MeCN in the presence of 3 equiv. of water. The generality of the reaction was investigated. For the β-substituent of α,β-unsaturated aldehyde (Table 1), not only electron-rich substituents such as *p*-tolyl, *p*-methoxyphenyl, and 3,4-dimethoxyphenyl substituents but also electron-deficient substituents such as *o*-fluorophenyl, *o*-chlorophenyl, *o*-bromophenyl, *p*-chloro, and *p*-bromophenyl substituents are suitable to afford products with excellent yield and diastereo-[17] and enantioselectivities. Heteroaromatic substituents such as furyl also afforded products with excellent results. The reaction also proceeded in the presence of 5 mol% of the catalyst **3a** in good yield with excellent enantioselectivity, although the reaction was slow. When we employ crotonaldehyde, a complex mixture was obtained. For the silyl enol ether (Table 2), not only silyl enol ether of cyclohexanone but also those of cyclopentanone and cycloheptanone can be employed successfully to afford the Michael products with excellent enantioselectivity although diastereoselectivity is moderate.

Table 1. The generality of the Michael reaction of α,β-unsaturated aldehyde in the asymmetric Michael reaction of silyl enol ether **6a**[a]



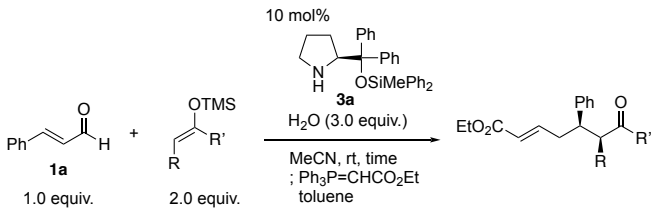
Entry	Ar	t [h]	*syn*/*anti*[b]	Yield [%][c]	Ee [%][d]
1	phenyl	6	6:1	97	99
2[e]	phenyl	24	5:1	89	96
3	2-naphthyl	5	5:1	99	96
4	*p*-MeC_6H_4	6	5:1	96	98
5	*p*-$MeOC_6H_4$	8	4:1	97	98
6	3,4-$(MeO)_2C_6H_3$	7	5:1	95	98
7	*o*-FC_6H_4	6	4:1	87	98
8	*o*-ClC_6H_4	8	2:1	89	99
9	*o*-BrC_6H_4	10	3:1	90	97
10	*p*-ClC_6H_4	4	4:1	91	98
11	*p*-BrC_6H_4	4	5:1	95	97
12	2-furyl	10	3:1	92	98

[a] Unless otherwise shown, the reaction was performed by employing α,β-enal (0.50 mmol), silyl enol ether **6a** (1.0 mmol), organocatalyst **3a** (0.050 mmol), water (1.5 mmol), in MeCN (0.50 mL) at room temperature. After the reaction, solvent was removed. Then, Wittig reagent (0.75 mmol) and toluene (0.50 mL) were added. See supporting information for details. [b] Determined by ^{1}H-NMR. [c] Yield of diastereomer mixtures. [d] Determined by HPLC analysis on a chiral column material. [e] Catalyst **3a** (0.025 mmol) was employed.

Once the reaction conditions of the asymmetric Michael reaction of silyl enol ether of cyclohexanone **6a** were determined, the Michael reaction of silyl dienol ether **5a** was examined. Because silyl dienol ether **5a** is labile compared with silyl enol ether **6a**, **5a** was decomposed under the best reaction condition of cyclohexanone **6a** at room temperature. Thus, the reaction was carried out at 0 °C, but the reaction was slow, affording the desired Michael product in low yield (Table 3, entry 1). After the screening of the reaction conditions (Table 3), good results were obtained, when 3 equiv of silyl dienol ether **5a** was employed in the presence of 20 mol% of the catalyst and 5 equiv of water (entry 4). It should be noted that the successive Michael reaction,

namely domino Michael/Michael reaction, does not proceed at all without the formation of a bicyclo[2.2.2]octanone derivative.

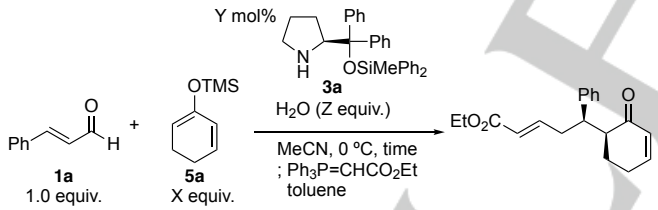
Table 2. The generality of the Michael reaction of silyl enol ether in the asymmetric Michael reaction of cinnamaldehyde[a]



Entry	Silyl enol ether	t [h]	*syn*/*anti*[b]	Yield [%][c]	Ee [%][d]
1		6	6:1	97	99
2		6	3:1	90	97
3		10	3:1	85	91

[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde **1a** (0.50 mmol), silyl enol ether (1.0 mmol), organocatalyst **3a** (0.050 mmol), water (1.5 mmol), in MeCN (0.50 mL) at room temperature. After the reaction, solvent was removed. Then, Wittig reagent (0.75 mmol) and toluene (0.50 mL) were added. See supporting information for details. [b] Determined by ^{1}H-NMR. [c] Yield of diastereomer mixture. [d] Determined by HPLC analysis on a chiral column material.

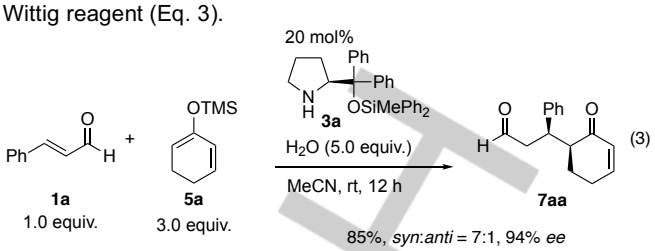
Table 3. The effect of amount of silyl enol ether, catalyst and water in the asymmetric Michael reaction of cinnamaldehyde and silyl dienol ether **5a**[a]



Entry	X [equiv] [b]	Y [mol%] [c]	Z [equiv] [d]	t [h]	*syn*/*anti*[e]	Yield [%][f]	Ee [%][g]
1	2	10	3	48	7:1	40	n.d.[h]
2	3	10	3	36	7:1	45	n.d.[h]
3	3	20	3	36	7:1	53	n.d.[h]
4	3	20	5	12	6:1	86	94

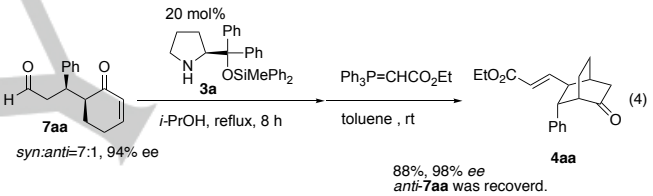
[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde **1a** (0.5 mmol), silyl dienol ether **5a** (X equiv.), organocatalyst **3a** (Y mol%), and water (Z equiv.) in MeCN (0.50 mL) at 0 °C. After the reaction, solvent was removed. Then, Wittig reagent (0.75 mmol) and toluene (0.50 mL) were added. See supporting information for details. [b] Amount of silyl enol ether. [c] Amount of organocatalyst **3a**. [d] Amount of water. [e] Determined by ^{1}H-NMR. [f] Yield of diastereomer mixtures. [g] Determined by HPLC analysis on a chiral column material. [h] n.d. = not determined.

Under the best reaction conditions, the Michael adduct **7aa** was isolated as its aldehyde form in 85% yield with excellent diastereo- and enantioselectivities without the treatment with Wittig reagent (Eq. 3).



85%, *syn*:*anti* = 7:1, 94% *ee*

Because the first Michael reaction of **1a** and silyl dienol ether **5a** proceeded to afford the Michael product **7aa** in good yield with excellent enantioselectivity, we then investigated the second Michael reaction. Although the second intramolecular Michael reaction did not proceed at all under the first Michael reaction conditions at 0 °C, we found that the second Michael reaction proceeded in the presence of the same catalyst **3a** at a higher temperature in a different solvent (*i*-PrOH). That is, when **7aa** was treated with diphenylprolinol silyl ether **3a** at reflux in *i*-PrOH, the bicyclo[2.2.2]octanone derivative **4aa** was obtained in good yield (88%) with excellent enantioselectivity (98% *ee*) with the recovery of *anti*-isomer **7aa** (Eq. 4). It should be noted that the enantioselectivity of the bicyclo[2.2.2]octanone derivative **4aa** is found to be higher (98% *ee*) than that of the first Michael product **7aa** (94% *ee*) *vide infra*.



syn:*anti*=7:1, 94% ee

88%, 98% *ee*
anti-**7aa** was recoverd.

The bicyclo[2.2.2]octanone derivative **4aa** was synthesized using two pots, in which the same catalyst **3a** was employed. One-pot operations are an effective method for both carrying out several transformations and forming several bonds in a single pot, while at the same time cutting out several purifications, minimizing chemical waste generation, and saving time.[9, 18] Next, we tried to make the two single-pot operations into one single-pot reaction. Although the best solvents in the first and second reactions are MeCN and *i*-PrOH, respectively, we found that the second reaction also proceeded efficiently in a mixed solvent of MeCN and *i*-PrOH. Thus, these two separate reactions can be combined in the same pot without a solvent switch. That is, after the first Michael reaction, the addition of *i*-PrOH and heating the reaction mixture under reflux conditions gave the bicyclo[2.2.2]octanone derivative **4aa** in good yield with excellent enantioselectivity after the treatment with $Ph_3P=CHCO_2Et$ (Table 4, entry 1). Compared with the two-pot reaction (0.85 × 0.88 = 0.75), the yield of the one-pot synthesis is little better (78%).

Once the reaction condition of the two-step, one-pot synthesis of chiral bicyclo[2.2.2]octanone derivatives **4** was established, the generality of the reaction was investigated (Table 4). For the β–substituent of α,β-unsaturated aldehyde, not only electron-rich aryls such as *p*-tolyl and *p*-methoxyphenyl groups but also electron-deficient aryls such as *p*-fluorophenyl, *p*-chlorophenyl, *p*-bromophenyl, and *m*-bromophenyl substituents are suitable to afford the products with excellent yield as a single isomer in a nearly optically pure form. Heteroaromatic substituents such as furyl also afforded a bicyclo[2.2.2]octanone

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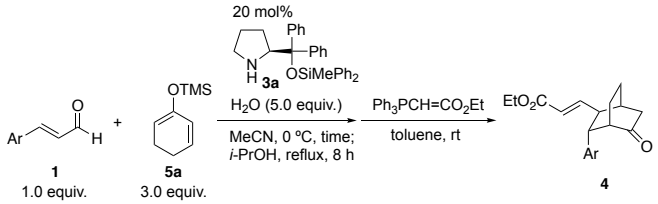
derivative with excellent enantioselectivity. It should be noted that only a single isomer was obtained in a nearly optically pure form in all the cases examined. In all cases, *anti*-isomer of the first Michael product is unreactive in the second Michael reaction. A complex mixture was obtained in the reaction of crotonaldehyde.

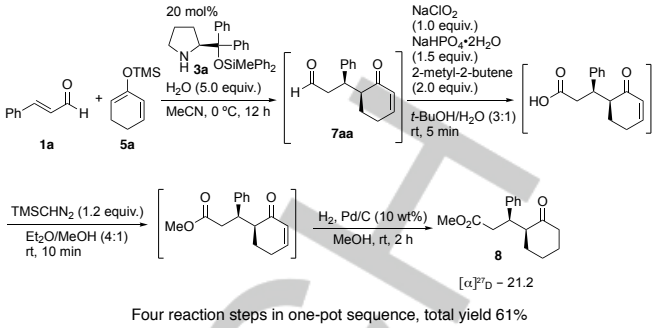
Table 4. The generality of the one-pot Michael/Michael reaction of silyl dienol ether **5a** and α,β-unsaturated aldehyde[a]



Entry	Ar	t [h]	Yield [%][b]	Ee [%][c]
1	phenyl	12	78	98
2	2-naphthyl	15	74	99
3	*p*-MeC_6H_4	18	76	99
4	*p*-$MeOC_6H_4$	10	74	99
5	*p*-FC_6H_4	10	75	99
6	*p*-ClC_6H_4	10	72	99
7	*p*-BrC_6H_4	12	73	99
8	*m*-BrC_6H_4	10	73	99
9	2-furyl	20	51	99

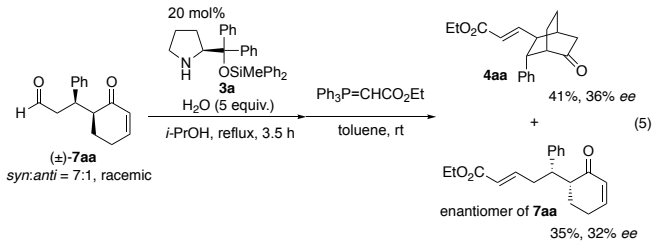
[a] Unless otherwise shown, the reaction was performed by employing α,β-enal (0.50 mmol), silyl dienol ether **5a** (1.0 mmol), organocatalyst **3a** (0.10 mmol), and water (2.5 mmol) in MeCN (0.50 mL) at 0 °C for indicated time. After the addition of *i*-PrOH (2.0 mL), a reaction mixture was stirred for 8 h at reflux temperature. After the reaction, solvent was removed. Then, Wittig reagent (0.75 mmol) and toluene (0.50 mL) were added. See supporting information for details. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral column material.

The absolute configuration of the Michael adduct of cinnamaldehyde **1a** and silyl enol ether **6a** was determined by comparison of the optical rotation with the reported value.[8] The absolute configuration of the first Michael product **7aa** of cinnamaldehyde **1a** and silyl dienol ether **5a** was determined as follows (Scheme 3). After the Michael reaction, the Michael adduct **7aa** was converted into a carboxylic acid by Kraus–Pinnick oxidation[19] in the same reaction vessel. Then, methyl ester formation with $TMSCHN_2$, followed by hydrogenation afforded **8**. Because **8** is a known compound,[20] the absolute configuration was determined by comparison of the optical rotation. It should be noted that **8** was synthesized from the Michael reaction of **1a** and **5a** in a single reaction vessel with a good yield based on the pot economy, although there are four reaction steps. The absolute configuration of **4aa** was assigned in analogy to that of **7aa**.



Scheme 3. The determination of the absolute configuration of **7aa** determined.

Because we are interested in the increase of the enantioselectivity from the first Michael reaction product **7aa** to the second Michael product **4aa**, we investigated the second Michael reaction in detail. We examined the second Michael reaction using the racemic material **7aa** with chiral diphenylprolinol silyl ether catalyst **3a** (Eq. 5). When we stopped the reaction after 3.5 h, which is shorter than Eq. 4, the product **4aa** was obtained in 41% yield with 36% *ee*, while the starting material was recovered in 35% yield with 32% *ee*, in which the opposite enantiomer was predominantly recovered. *anti*-Isomer of **7aa** was also recovered. From these results, diphenylprolinol silyl ether **3a**, a chiral amine, affects the enantioselectivity in the second intramolecular Michael reaction. Thus, it is clear that kinetic resolution occurs in the second Michael reaction, and the minor enantiomer does not react readily (S value is 3.1, see SI). Although the S value in the kinetic resolution of the second step is not so large, it is enough to increase the enantioselectivity of **4aa** from 94% *ee* to 99% *ee*. Moreover, the *anti*-isomer in the first Michael reaction did not react in the second Michael reaction. Thus, in the two successive Michael reactions, the same chiral catalyst **3a** acts positively, increasing both diastereo- and enantioselectivities to afford the bicyclo[2.2.2]octanone derivatives **4** as a single isomer in nearly optically pure form.



In summary, asymmetric catalytic Mukaiyama Michael reaction of the silyl enol ether of a cyclic ketone and α,β-unsaturated aldehyde proceeds efficiently, catalyzed by diphenylprolinol silyl ether to afford the Michael products with excellent diastereo- and enantioselectivities. Dienol silyl ether also can be employed as a Michael donor in the Mukaiyama Michael reaction to afford the Michael product with excellent enantioselectivity. The second intramolecular Michael reaction is also catalyzed by the same diphenylprolinol silyl ether to afford the bicyclo[2.2.2]octanone derivatives in nearly optically pure form, higher than the first Michael reaction, in which kinetic resolution occurred. These two reactions can be combined into a one-pot operation. Thus, a two-step, one-pot sequential Mukaiyama Michael reaction and intramolecular Michael reaction of dienol silyl ether and α,β-unsaturated aldehyde proceeds,

catalyzed by diphenylprolinol silyl ether to afford the bicyclo[2.2.2]octanone derivatives as a single isomer in nearly optically pure form.

Acknowledgements

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Keywords: asymmetric reaction • Mukaiyama Michael reaction • organocatalyst • one-pot reaction • kinetic resolution

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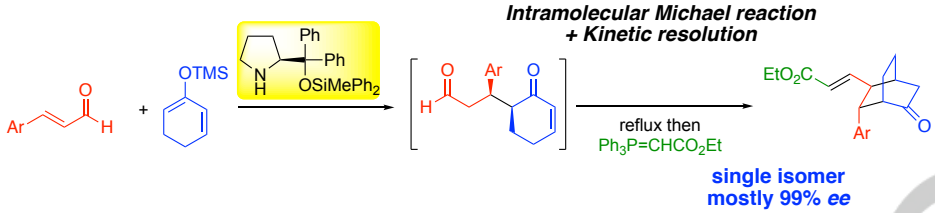

Synthetically useful chiral bicyclo[2.2.2]octanone derivatives can be synthesized with excellent diastereo- and enantioselectivity via a two-step, one-pot reaction using diphenylprolinol silyl ether as an effective organocatalyst, where positive kinetic resolution occurred to generate the desired compounds in a nearly optically pure form.

Key Topic: Organocatalytic domino reaction