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Diphenylprolinol Silyl Ether Catalysis in an Asymmetric Formal Carbo [3 + 3] Cycloaddition Reaction via a Domino Michael/Knoevenagel Condensation

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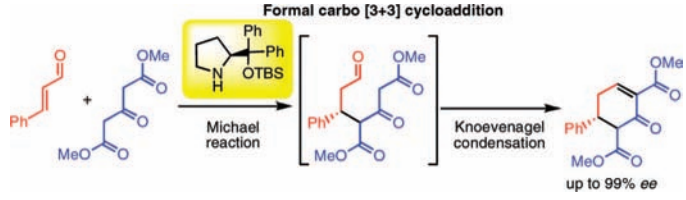
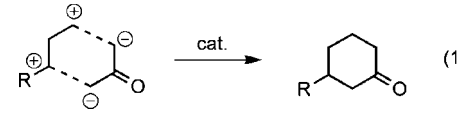
ABSTRACT



Diphenylprolinol silyl ether was found to catalyze the formal carbo [3 + 3] cycloaddition reaction through the domino reaction via the Michael reaction, followed by Knoevenagel condensation of the α,β-unsaturated aldehyde and dimethyl 3-oxopentanedioate, affording substituted cyclohexenone derivatives with excellent enantioselectivity.

The cyclohexane ring system is one of the most common structures in natural products and biologically significant molecules. The Diels−Alder reaction ([4 + 2] cycloaddition) is one of the most widely employed methods for the construction of this ring system with control of the relative and absolute configuration, and there are several asymmetric catalytic Diels−Alder reactions promoted by chiral Lewis acids.[1] Recently, organocatalysts have been successfully applied to this enantioselective reaction.[2] The carbo [3 + 3] cycloaddition is another useful method for the synthesis of the cyclohexane ring (eq 1). As for the aza [3 + 3] cycloaddition reaction, we have recently reported the first asymmetric formal aza [3 + 3] cycloaddition for the formation of the piperidine ring system.[3−5] Carbo [3 + 3] cycloaddition, however, is very rare, and there are only two enantioselective, catalytic versions[6] to the best of our knowledge.



Recently, the field of organocatalysis has been developing rapidly, and many kinds of new organocatalysts have been

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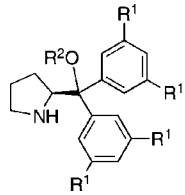
reported.[7] Diarylprolinol silyl ethers,[8] which have been developed independently by our group[9] and Jørgensen's group,[10] have been successfully utilized by several research groups (Figure 1). We have reported the [4 + 2] cycloaddition reaction using diarylprolinol silyl ethers as organocatalysts.[2e,f] We have applied diphenylprolinol silyl ether to the reaction of α,β-unsaturated aldehydes with dimethyl 3-oxopentanedioate to find that a formal carbo [3 + 3] cycloaddition reaction proceeds in a highly enantioselective manner, which will be described in this paper.

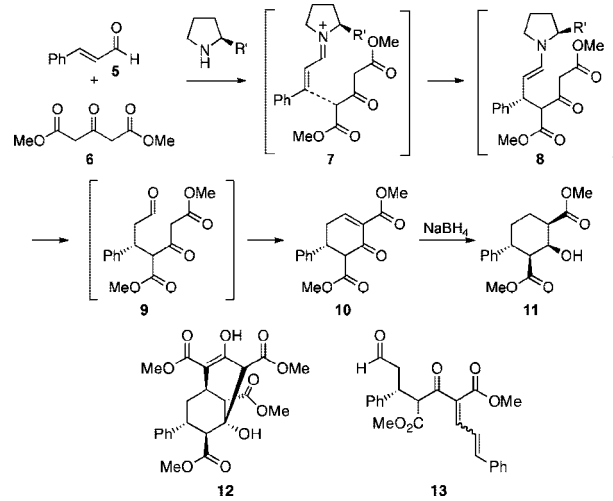


catalyst	R^1	R^2
1	H	TMS
2	H	TBS
3	CF_3	TMS
4	H	H

Figure 1. Organocatalysts examined in the present study.

The domino reaction is a powerful method for the construction of complex molecules in a single process,[11] and there are several successful organocatalysis-mediated domino reactions.[12] We expected that the formal carbo [3 + 3] cycloaddition reaction would proceed between an α,β-unsaturated aldehyde and 3-oxopentanedioate via the domino reaction of the Michael reaction and hydration of the resulting enamine followed by a Knoevenagel condensation reaction. Our scenario is as follows (Scheme 1). An amine catalyst and α,β-unsaturated aldehyde **5** could generate an iminium ion, which would react with dimethyl 3-oxopentanedioate **6** to generate enamine **8** by an enantioselective Michael reaction. Hydration occurs to afford aldehyde **9**, and an intramolecular Knoevenagel condensation reaction would proceed to provide the functionalized cyclohexenone derivative **10**. It should be noted that Jørgensen and co-workers reported the synthesis of a chiral cyclohexenone derivative from *tert*-butyl 3-oxobutyrate and an α,β-unsaturated aldehyde in the presence of diarylprolinol silyl ether, followed by treatment with TsOH under reflux conditions.[13] During the preparation of this manuscript, Jørgensen and co-workers reported the domino reaction using the same starting materials **5** and **6**, affording the 2:1 addition product **12** with excellent enantioselectivity without formation of the 1:1 addition product.[14]

Scheme 1. Enantioselective Domino Reaction of **5** and **6**



The reaction of cinnamaldehyde and dimethyl 3-oxopentanedioate **6** was selected as a model, and the reaction was investigated in detail. We soon found that the molar ratio of the reagents is very important: when 1.5 equiv of tricarbonyl compound **6** was used, the desired product was not formed; instead, the bicylo[3.3.1]nonene derivative **12** was generated as a single isomer in 51% yield, which is the main product obtained by Jørgensen and co-workers.[14] When 0.5 equiv of **6** was employed, diene derivative **13** was isolated in 55% yield, which would be generated by the overreaction of the Michael product **9** with another cinnamaldehyde via Knoevenagel condensation. This result indicates that the intermolecular Knoevenagel condensation is faster than hydration of the enamine **8**.

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(12) For selected examples of organocatalytic asymmetric domino reactions, see: (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (b) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (c) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (d) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (f) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (g) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (h) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965. (i) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (j) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202. (k) Hazelard, D.; Ishikawa, H.; Hashizume, D.; Koshino, H.; Hayashi, Y. *Org. Lett.* **2008**, *10*, 1445.

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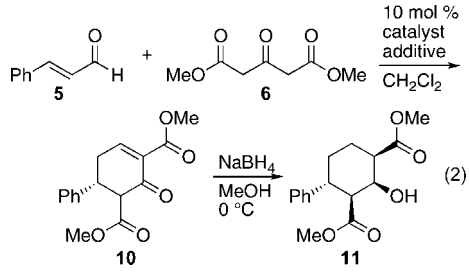
(14) Bertelsen, S.; Johansen, R. L.; Jørgensen, K. A. *Chem. Commun.* **2008**, 3016.

Despite these unsuccessful results, the desired product was formed when an equimolar amount of reagents **5** and **6** was employed. That is, when **5** and **6** were treated with diphenylprolinol trimethylsilyl ether **1** in toluene, the desired cyclohexenone **10** was formed, which was isolated as the corresponding alcohol **11** as a single isomer in 35% yield over two steps after reduction with $NaBH_4$ (Table 1, entry 1). Studies of the effect of the solvent showed that CH_2Cl_2 was suitable. It was found that a small excess of tricarbonyl compound **6** (1.1 equiv) increased the yield to 58% with excellent enantioselectivity (92% ee, entry 2). Next, the influence of catalyst choice was investigated, and the results are summarized in Table 1.

Table 1. Optimization of the Reaction Conditions[a]



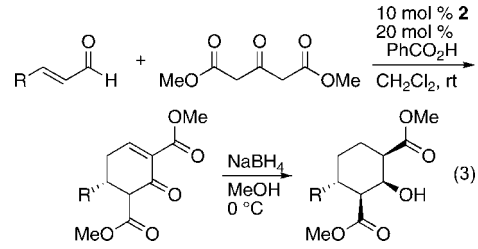
entry	catalyst	additive	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**1**		4	35	nd[e]
2	**1**		1	58	92
3	**2**		22	58	94
4	**3**		48	52	92
5	**4**		52	17	−50
6	**2**	CH_3CO_2H	3	34	94
7	**2**	$PhCO_2H$	1	75	95
8	**2**	CF_3CO_2H	2	0	nd[e]

[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde (0.5 mmol), dimethyl 3-oxopentanedioate (0.55 mmol), and organocatalyst (0.05 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for the indicated time. The reaction mixture was treated with $NaBH_4$ at 0 °C, and the product was isolated as an alcohol **11**. [b] Isolated yield of **11**. [c] Determined by HPLC analysis on a chiral phase. [d] Dimethyl 3-oxopentanedioate (0.50 mmol) was employed in toluene. [e] nd = not determined.

The reaction was slow, and the opposite enantiomer was generated in low yield with moderate enantioselectivity in the presence of diphenylprolinol **4**, which does not contain a siloxy group (entry 5). Although trifluoromethyl-substituted diarylprolinol silyl ether **3** gave excellent enantioselectivity, the reaction was slow (48 h, entry 4). Among the catalysts examined, the *tert*-butyldimethylsilyl ether of diphenylprolinol **2** was the choice (94% ee, entry 3). Further optimization was performed with an additive to increase the yield, which showed that benzoic acid is effective, providing the desired alcohol **11** as a single isomer in a short time (1 h) and good yield with excellent enantioselectivity (75%, 95% ee, entry 7).

After the reaction conditions were optimized, the generality of the reaction was investigated, and the results are summarized in Table 2. The reaction has broad applicability. Not only phenyl but also a 2-naphthyl-substituted acrolein

Table 2. Catalytic Asymmetric Formal Carbo [3 + 3] Cycloaddition Reaction of Dimethyl 3-Oxopentanedioate and α,β-Unsaturated Aldehydes[a]



entry	R	time (h)	yield[b] (%)	ee[c] (%)
1	phenyl	1	75	95
2[d]	phenyl	14	68	95
3	2-naphthyl	1.5	70	>99
4	*p*-nitrophenyl	0.5	74	99
5	*p*-bromophenyl	1	77	99
6	*p*-chlorophenyl	1	71	96
7	*p*-methoxyphenyl	2	65	94
8	2-furyl	1	63	97

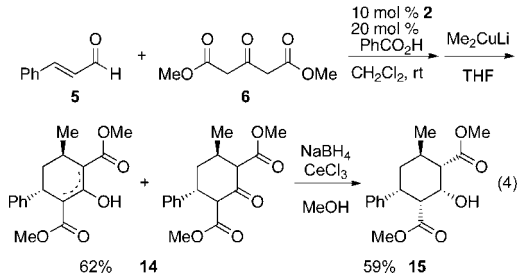
[a] Unless otherwise noted, the reaction was performed by employing α,β-unsaturated aldehyde (0.5 mmol), dimethyl 3-oxopentanedioate (0.55 mmol), organocatalyst **2** (0.05 mmol), and benzoic acid (0.1 mmol) in dichloromethane (1.0 mL) at room temperature for the indicated time. The reaction mixture was treated with $NaBH_4$ at 0 °C. [b] Isolated yield of alcohol (two steps). [c] Determined by HPLC analysis on a chiral phase. [d] Organocatalyst **2** (2 mol %) and $PhCO_2H$ (4 mol %) were employed.

derivative gave an excellent result (entry 3). When the substituent is electron deficient, such as *p*-nitro-, *p*-bromo-, or *p*-chlorophenyl, the reaction also proceeds efficiently, generating the [3 + 3] cycloadducts with excellent enantioselectivities (entries 4−6). Although the reaction is a little slower for acrolein derivatives possessing electron-rich aromatic substituents such as *p*-methoxyphenyl, a good yield was obtained with excellent enantioselectivity (entry 7). Not only aromatic groups but also heteroaromatic groups such as furyl are suitable substituents (entry 8). Although we used 10 mol % of the catalyst, the catalyst loading can be reduced to 2 mol %. That is, in the presence of 2 mol % of **2** and 4 mol % of benzoic acid, the reaction of cinnamaldehyde proceeded efficiently, affording the [3 + 3] cycloaddition product in 68% yield without compromising the enantioselectivity (95% ee) (entry 2). As for the aliphatic enals, we could not get a good result.

The formal [3 + 3] cycloaddition product **10** is synthetically useful, because it possesses several functional groups, including a double bond activated with two electron-withdrawing groups such as keto and ester moieties. Further one-pot transformations were investigated, and the following three examples are successful transformations of this key intermediate **10** to the more functionalized cyclohexanone derivatives in the same pot without isolation of the intermediate.

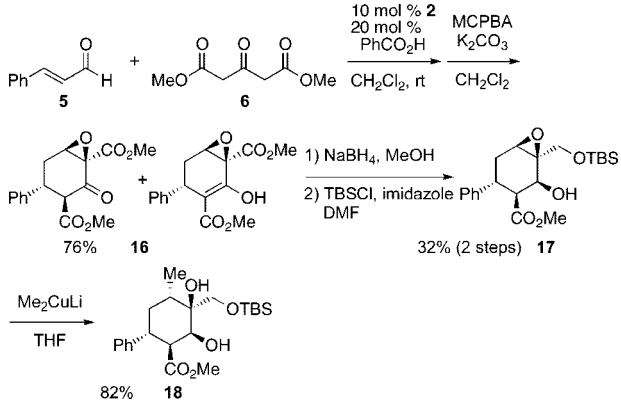
A THF solution of Me_2CuLi was added to the reaction mixture of cinnamaldehyde **5**, dimethyl 3-oxopentanedioate **6**, a catalytic amount of catalyst **2**, and benzoic acid. The Michael reaction proceeded in a diastereoselective manner

to generate the methyl addition product with a mixture of keto and enol forms, **14**. Reduction with $NaBH_4$ in the presence of $CeCl_3$[15] afforded the highly substituted cyclohexanol **15**, the relative configuration of which was determined by the analysis of its NOESY spectra. The newly generated stereochemistry of the methyl group was obtained as a single isomer, as shown in eq 4.

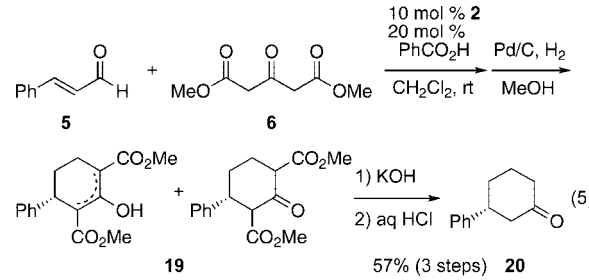


Another transformation is the one-pot formation of epoxide **16**. Addition of *m*-CPBA and K_2CO_3 to the reaction pot of the formal [3 + 3] cycloadduct produced epoxycyclohexanone **16** in 76% yield as a single isomer. The epoxide **16** was further converted into the more functionalized cyclohexanol **18** as shown in Scheme 2, in which the relative stereochemistry was determined by the coupling constant and NOE analysis. This transformation indicates that the formal carbo [3 + 3] cycloaddition reaction is a powerful method for the synthesis of a highly substituted cyclohexane framework.

Scheme 2. Synthesis of Functionalized Cyclohexane Derivatives Based on the Formal [3 + 3] Cycloaddition Reaction



After the [3 + 3] cycloaddition reaction, the solvent was removed under reduced pressure, MeOH and a catalytic amount of Pd/C were added, and the reaction was performed under H_2 atmosphere using the same reaction pot (eq 5). Cyclohexanone **19** was obtained, which was treated with KOH and then with acid to afford 3-substituted cyclohexanone **20** in 57% yield over three steps. This is one of the most facile syntheses of chiral 3-substituted cyclohexanones,[13,16] and it also indicates the absolute configuration of **20** by comparison of the optical rotation with that of the literature.[17]



In summary, we have developed a highly enantioselective formal carbo [3 + 3] cycloaddition reaction of α,β-unsaturated aldehydes and dimethyl 3-oxopentanedioate catalyzed by diphenylprolinol silyl ether as an organocatalyst via the domino reaction of the Michael reaction/Knoevenagel condensation. The cyclohexenone derivatives that are generated are useful synthetic intermediates with several functional groups, and excellent enantioselectivities are obtained in most of the reactions. This is one of the rare successful enantioselective, catalytic formal carbo [3 + 3] cycloaddition reactions for formation of the cyclohexene structure. It should also be noted that the reaction is high yielding and clean and that further one-pot reactions with other reagents can be performed, which can construct complex cyclohexanones via formation of several bonds in a single pot.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^1H NMR, ^{13}C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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