Construction of Acyclic All-Carbon Quaternary Stereocenter Based on Asymmetric Michael Addition of Chiral Amine

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Introduction

The asymmetric construction of quaternary stereocenters is one of the most important themes in synthetic organic chemistry because quaternary chiral units are present in many biologically and pharmaceutically active compounds. A number of methods for the construction of quaternary stereocenters have been reported to date. Among the quaternary stereocenters, all-carbon quaternary stereocenters consisting of four types of carbon substituents are particularly difficult to synthesize because highly congested structures hamper the access of reagents or catalysts to the reaction site. Numerous studies on the asymmetric synthesis of all-carbon quaternary stereocenters have been carried out. In those studies, however, stereoselective control in the formation of all-carbon quaternary stereocenters is more difficult in acyclic systems than cyclic systems due to the conformationally flexible transition state in the acyclic systems. Thus, extensive efforts have been made to develop a method for the formation of acyclic all-carbon quaternary stereocenters. The utilization of an enolate is one of the most powerful methods for the construction of acyclic all-carbon quaternary stereocenters. Effective methods that use the nucleophilicity of enolates have been reported.

We have developed an asymmetric Michael addition reaction of chiral amine I having a bornyl group as a chiral auxiliary, in which the construction of multiple contiguous chiral centers has been achieved by taking advantage of the enolate intermediate derived from the asymmetric Michael addition of an α,β-unsaturated ester utilizing this protocol. Bolstered by our findings, we anticipated that an effective method for the synthesis of acyclic all-carbon quaternary stereocenters would be developed by an alkylation of enolate intermediates. We have recently reported two contiguous chiral centers generated by the face-selective protonation of enolate intermediates, which were formed by the asymmetric Michael addition reaction of a chiral lithium amide with trisubstituted α,β-unsaturated esters. The present face-selective alkylation was able to employ diverse alkyl halides as an electrophile to afford various Michael adducts having an all-carbon quaternary stereocenter. With regard to the deprotection of the chiral auxiliary, N-iodosuccinimide used in our previous study did not work in the present cases; however, we found that pyridine iodine monochloride in the presence of HClO4 was effective to remove the bornyl group and the benzyl group on the amino group to provide the β-amino ester derivative.

Key words all-carbon quaternary stereocenter; asymmetric Michael addition; chiral amine; face-selective alkylation; trisubstituted α,β-unsaturated ester; β-amino ester
Results and Discussion

In the asymmetric construction of acyclic all-carbon quaternary stereocenters by the alkylation of the enolate intermediate, it is necessary to use geometrically pure trisubstituted (E)-α,β-unsaturated esters as the Michael acceptor to achieve high stereoselectivity. In this regard, we have recently developed a practical and E-stereoselective synthesis of various trisubstituted α,β-unsaturated esters, which has enabled us to use pure trisubstituted (E)-α,β-unsaturated esters in the present study(50,51) (Chart 2).

First, in order to establish the optimal reaction conditions, we examined the alkylation with benzyl bromide of enolate intermediate A, which was formed by the asymmetric Michael addition reaction of 1-Li with α,β-unsaturated ester 2a in tetrahydrofuran (THF) at −50 °C. Contrary to our expectation, desired Michael adduct 4a having the all-carbon quaternary stereocenter was generated in low yield (22% yield), and Michael adduct 3a was produced by the protonation of intermediate A in 54% yield (Table 1, entry 1). It is known that a lithium salt forms the aggregation, which affects the nucleophilicity of the counter anion. In fact, we observed that a change of aggregation by the addition of an additive such as hexamethylphosphoramide (HMPA) controlled the reactivity of 1-Li(45). Thus, we examined the effect of an additive.

The benzylation of enolate intermediate A in the presence of HMPA (1.5 equivalent (equiv)) at −50 °C in THF afforded 4a having the all-carbon quaternary stereocenter in 90% yield with high diastereoselectivity (major isomer/minor isomers = 97 : 3) (Table 1, entry 2). Interestingly, both yield and stereoselectivity of 4a were not changed despite the use of an excess amount of HMPA (5.0 equiv) (Table 1, entry 3). It seemed that the partial interaction between lithium cation and enolate intermediate A remained, so that high stereoselectivity was achieved.

Having established the optimal conditions for a series of reactions, we next explored the substrate species (Table 2). In the benzylation reactions that used Michael acceptors 2b...
and 2c, which have an electron-withdrawing group and an electron-donating group on the aromatic ring, respectively, we obtained desired Michael adducts 4b and 4c in excellent yields with high diastereoselectivities (Table 2, entries 2 and 3). Then, electrophiles other than benzyl bromide were examined. The allylation of enolate intermediate A by using allyl iodide provided adduct 4d in 86% yield with the diastereomeric ratio of 93:7 (Table 2, entry 4). Moreover, the reaction that used ethyl iodide as the electrophile, which gave poor results in the method reported by Davies et al.,29) successfully proceed to afford ethylated adduct 4e in 90% yield with the diastereomeric ratio of 96:4 (Table 2, entry 5). It should be noted that our enolate intermediate A worked not as a base but as a potent nucleophile and therefore, crucial side reactions, such as the β-elimination of ethyl iodide, did not take place. In addition, the methylation of enolate intermediates derived from Michael acceptor having a bulkier substituent, such as a benzyl or an ethyl group, at the α position gave desired adducts 4f and 4g in good to excellent yields with high diastereoselectivities (Table 2, entries 6 and 7).

The absolute configuration of major isomer 4 was confirmed by the X-ray diffraction analysis of crystalline Michael adduct 4e52) (Fig. 1). The stereochemistry of the other major Michael adducts 4a-d, f and g were speculated as being the same from the comparison with the 1H-NMR spectra of the major Michael adduct 4e.53)

On the basis of both the results of the above X-ray analysis of 4e and knowledge from our previous reports,46,48) we show a plausible transition state of the present reaction in Fig. 2. The asymmetric Michael addition reaction would proceed via a six-membered ring transition state formed by coordinating lithium ion to the carbonyl oxygen of the substrate, where the Z-enolate intermediate would be generated from the Michael addition reaction of 1 with 2 having s-cis conformation as reported in the literature.54,55) Subsequent face-selective alkylation of the enolate intermediate would preferentially occur from the bottom face of the enolate intermediate due to steric repulsion by the N-benzyl group on the amino group. This selectivity is consistent with the face-selective protonation of the enolate intermediate in our previous report.48)

Finally, we tried to convert Michael adduct 4 into β-amino ester derivative 5 by removing both the bornyl group and the benzyl group on the amino group. We expected that β-amino ester derivatives 5 would be obtained easily by treatment of 4 with N-iodosuccinimide (NIS), as in our previous studies45–48,56) however, desired compound 5b was not formed because of an unexpected side reaction (Table 3, entry 1).

We employed pyridine iodine monochloride (ICl Py) instead of NIS, and the reaction gave desired product 5b in moderate yield (40%) (Table 3, entry 2). Further examination revealed that the addition of H2O (2.3 equiv) increased the yield of 5b (52%) (Table 3, entry 3). This result suggested that the hydrolysis of an iminium (or imine) intermediate, which was formed by the oxidation of the amino group with ICl Py, would be facilitated in the presence of an appropriate amount of water.45,57) Meanwhile, use of an excess amount of H2O (5

<table>
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<th>Entry</th>
<th>Reagent</th>
<th>H2O (eq)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>NIS (10)</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>ICI Py (10)</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>ICI Py (10)</td>
<td>2.3</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>ICI Py (10)</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>ICI Py (5)</td>
<td>—</td>
<td>trace</td>
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equiv) and reducing the amount of ICl Py to 5 equiv resulted in low product yields (45% and trace yields, respectively) (Table 3, entries 4 and 5). Side reactions were not observed when a minimum amount of water was added into the reaction mixture.

**Conclusion**

We succeeded in the construction of acyclic all-carbon quaternary stereocenters by utilizing the face-selective alkylation of enolate intermediate A. Enolate intermediates A, which were formed by the asymmetric Michael addition of 1-Li with α,β-unsaturated esters 2, were alkylated with high stereo-selectivity by diverse alky halides in the presence of HMPC to afford Michael adducts 4 having the all-carbon quaternary stereocenter. In the course of our study on the conversion of Michael adduct 4 into β-amino ester 5, we found that ICl Py in the presence of H2O was effective for the deprotection of Michael adduct 4b by the oxidative C–N bond cleavage reaction to afford desired β-amino ester 5b. Further studies on the asymmetric synthesis of various β-amino esters having the all-carbon quaternary stereocenter and a practical application of the present method to the synthesis of biologically active compounds are in progress and will be published elsewhere.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Supplementary Materials**

The online version of this article contains supplementary materials.

**References and Notes**


52) Crystal data of Michael adduct 4e were deposited in the Cambridge Crystallographic Data Center (CCDC 2079651).

53) Common characteristic peak, which was assigned to one of two methyl groups on the bornyl group, appeared at δ 0.87–0.91 ppm in $^1$H-NMR spectrum of the major Michael adduct 4a–e. Meanwhile, Michael adducts 4f and g, which were one of the minor isomers of Michael adducts 4a and e, have the similar characteristic peak as the Michael adduct 4a–e at δ 0.73–0.78 ppm in the $^1$H-NMR spectrum.


