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# Asymmetric Aldol Reaction of Allenoates: Regulation for the Selective Formation of Isomeric Allenyl or Alkynyl Aldol Adduct

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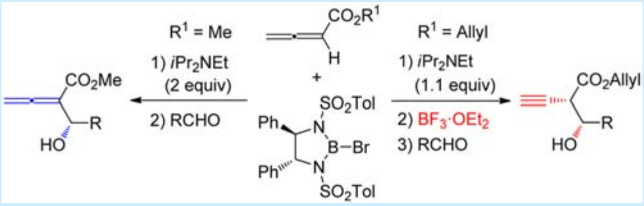
Ⓢ *Supporting Information*

**ABSTRACT:** A highly stereoselective synthesis of 3-butynyl-*threo*-aldol adducts is achieved from the reaction of allyl allenoate with a chiral bromoborane in the presence of *i*Pr$_2$NEt, followed by addition of BF$_3$·OEt$_2$ as an additive to scavenge excess base and then aldehydes, whereas isomeric allenyl aldol adducts are formed in the absence of a Lewis acid additive from methyl allenoate.



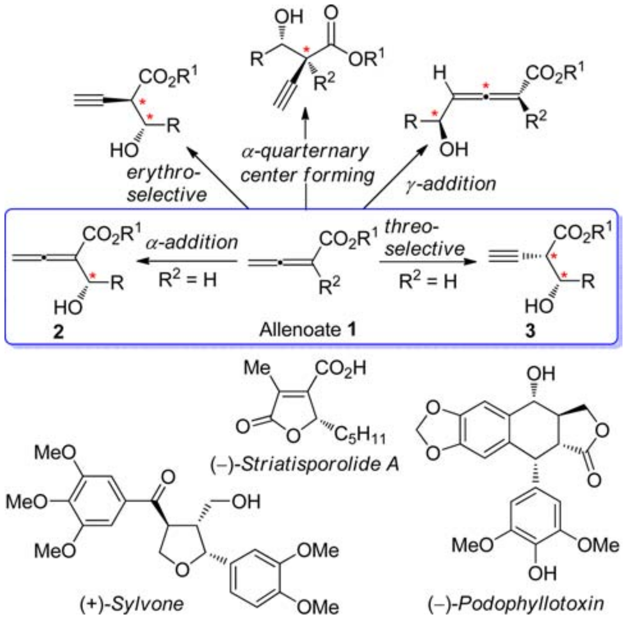
The discovery of efficient asymmetric methods to achieve the synthesis of enantiomerically pure compounds is of considerable interest in organic chemistry.[1] In light of widespread advances in asymmetric methods, aldol reactions of carbonyl functionalities using chiral auxiliaries or catalysts led to significant developments in the area of asymmetric synthesis.[2] Numerous successful methodologies using stoichiometric amounts of chiral reagents[3] and catalytic amounts of chiral Lewis acids,[4] bases,[5] and organocatalysts[6] have been developed and applied to organic synthesis. Although there have been many reports regarding the enhancement of chemical processes for practical use, the scope of aldol reactions is still limited to simple systems.

In our continuous efforts to utilize allenyl functionality, we have disclosed our discoveries of the synthetic methods for the construction of cyclic or acyclic systems through allylic transfer reactions to the carbonyls and imine equivalents.[7] The characteristic features of our approaches in terms of structural aspects of the products have encouraged us to carry out more investigations for designing new asymmetic routes using allenyl substrates. In this regard, we became quite interested in exploring stereo- and regioselective aldol routes starting from allenoate **1** to a variety of products possessing versatile functional groups (Scheme 1).[8]

Allenoates have been regarded as an attractive substrate for various chemical transformations and have gained much attention for synthetic utility because of their structural and chemical uniqueness with facile availability.[9] The most recent notable advances are Lewis base catalyses of allenoates utilizing amine or phosphine nucleophilic catalysts with a variety of electrophiles, including carbonyl equivalents, to provide structurally diverse cyclic products through formal cycloaddition processes.[10]

We report herein our discovery of control elements to regulate selective formation of isomeric allenyl **2** or 3-butynyl **3** aldol adducts from aldol reaction of allenoate **1** with aldehydes, which allows reactions in good yields with high levels of stereoselectivity (Scheme 1). To the best of our knowledge, there has been no report of stereoselective synthesis of aldol adducts such as allenyl **2** and 3-butynyl **3** from allenoate **1**.[11] Furthermore, synthetic applications can be foreseen for the products to give a variety of bioactive substances (Scheme 1).

**Scheme 1. Design of Allenoate Aldol Routes and Targets**



The first study focusing on the use of allenoates **1**[12] as suitable substrates for chemical conversions is depicted in Scheme 1. Our initial studies were carried out with chiral borane reagents such as Ipc$_2$BX (**4a**,**b**)[13] and **4c**[14] for the asymmetric aldol process. The choice of the chiral borane reagents **4** was based on the availability of both enantiomeric forms and their efficiency to promote the addition of various nucleophiles to carbonyl derivatives. Initial attempts to react **1** (R = Me) with **4a** (X = Br) in the presence of *i*Pr$_2$NEt at −78 °C followed by an addition

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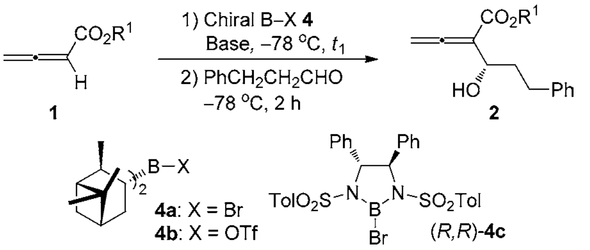
of hydrocinnamaldehyde indicated that the conversion to adduct **2a** could not be realized under various conditions. Replacement of **4a** with more reactive **4b** (X = OTf) also turned out to be unpromising, presumably due to geometrical difficulty of forming a boron enolate from allenoate with structurally complex **4b**. We found that **4c** could be an effective chiral reagent for this purpose. Initial experiments on the enolization of **1a** with **4c** in the presence *i*$Pr_2NEt$ at −78 °C for 1 h, followed by treatment with hydrocinnamaldehyde at −78 °C for 2 h, afforded encouraging but marginal results. Although aldol adduct **2a** was produced during the reaction as a single adduct, the problem of low chemical yield (40%) remained (entry 3). After surveying numerous conditions, we observed that the enolization time ($t_1$) was a crucial factor for optimal conditions (Table 1, entries 4−7).

**Table 1. Optimization for the Conversion of 1 to 2**



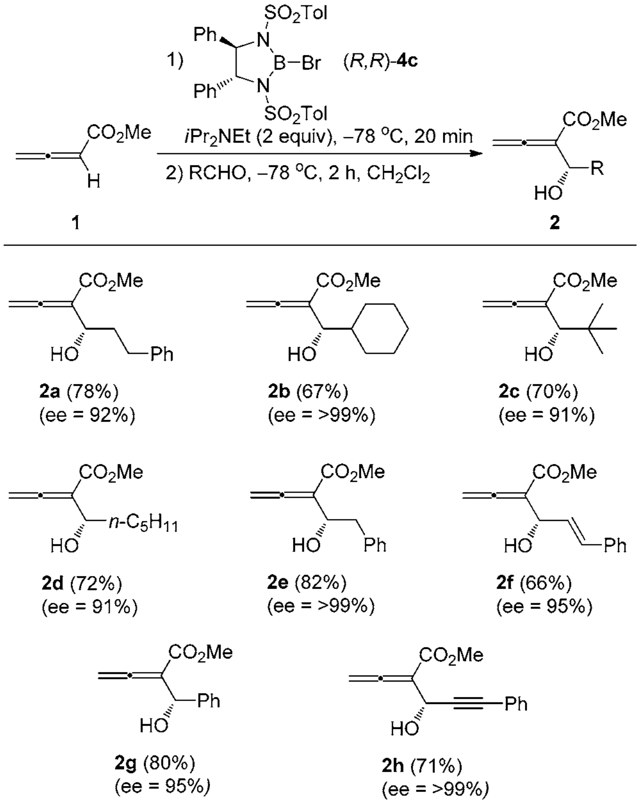
| entry | 4 | $R^1$ | base[a] | $t_1$[b] (h) | solvent | yield[c] (%) | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | Me | *i*$Pr_2NEt$ | 1 | $CH_2Cl_2$ | | |
| 2 | **4b** | Me | *i*$Pr_2NEt$ | 1 | $CH_2Cl_2$ | | |
| 3 | **4c** | Me | *i*$Pr_2NEt$ | 1 | $CH_2Cl_2$ | 40 | 90 |
| 4 | **4c** | Me | $Et_3N$ | 1 | $CH_2Cl_2$ | 21 | |
| 5 | **4c** | Et | *i*$Pr_2NEt$ | 1 | $CH_2Cl_2$ | 47 | 88 |
| 6 | **4c** | Me | *i*$Pr_2NEt$ | 1 | toluene | 23 | 84 |
| 7 | **4c** | Me | *i*$Pr_2NEt$ | 0.3 | $CH_2Cl_2$ | 78 | 92 |

[a] Using 2 equiv. [b] Enolization time. [c] Yields are those of products isolated after purification by chromatography. [d] Determined by analysis of HPLC.

During optimization studies, several key findings emerged (entry 7): (1) about 20 min of the enolization time at −78 °C resulted in the best chemical yields; (2) *i*$Pr_2NEt$ (2 equiv) proved to be a suitable base compared to other bases such as $Et_3N$ and *N*-methylpyrrolidine for this transformation; (3) reactions performed in $CH_2Cl_2$ resulted in the best chemical yields in comparison with other solvent systems including toluene; (4) methyl allenoate is superior to ethyl allenoate in terms of chemical yield and enantioselectivity; (5) reactions always produced *α*-addition adduct **2a** as a sole product. Under optimal conditions, the reaction of **1** ($R^1$ = Me) with hydrocinnamaldehyde in $CH_2Cl_2$ produced **2a** in 78% yield with 92% ee.

With the notion that this approach might lead to a general and efficient method for the synthesis of **2**, we set out to explore structurally varying aldehydes to extend the reaction scope. Indeed, the method turned out to be successful with structurally various aldehydes (1°, 2 °, 3 °, Ar, enal, and ynal) forming exclusively *α*-addition aldol products **2** in moderate to good yields with high levels of enantioselectivity, as can be seen in Scheme 2.

**Scheme 2. Allenoate Aldol Reaction of 1 ($R^1$ = Me) to 2[a]**



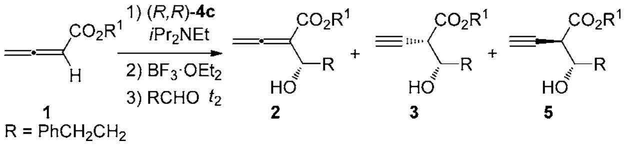
[a] For conditions, see Table 1.

In an effort to expand the scope of chemical transformation in the synthesis of **2** from allenoate **1**, we have focused on the design of a reaction pathway to produce *threo*-**3** or *erythro*-**5** selectively, which are prone to isomerization and, therefore, more difficult to isolate compared to **2**. From a mechanistic perspective for the formation of **2**, two major events are immediately discernible in the reaction process. The first event is presumably the aldolization mediated by **4c** and *i*$Pr_2NEt$ between allenoate **1** and the aldehyde, which produces 3-butynyl aldol adduct **3**. The second step of the reaction would be the isomerization of alkyne **3** to allene **2**. In general, the isomerization from **3** to more stable *α*,*β*-unsaturated allenoate **2** is predictable. We reasoned that if **3** is an intermediate toward the formation of **2**, then it might be possible to isolate **3** by developing a method to prevent the isomerization. Note that structures related to 3-butynyl aldol adducts **3** and **5** have not been reported in the literature.

With this issue in mind, our investigations began by reducing the amount of *i*$Pr_2NEt$ because the isomerization was attributed to the use of excess base during the reaction. Initial attempts for reaction of **1** ($R^1$ = Et) with **4c** in the presence of *i*$Pr_2NEt$ (1 equiv) under the same conditions and then with hydrocinnamaldehyde for 10 min at −78 °C indicated that the conversion to the desired 3-butynyl adducts **3** and **5** turned out to be only marginal. Reaction always produced **2** ($R^1$ = Et) as a major component along with the 3-butynoate aldol adducts **3** and **5** as minor products in 36% combined yields (Table 2, entry 2).

We subsequently speculated that the prevention of isomerization might require a Lewis acid additive to scavenge the base effectively. After screening reaction conditions with potent Lewis acids such as $BF_3{\cdot}OEt_2$, $B(OMe)_3$, and $Al(OEt)_3$, we found that $BF_3{\cdot}OEt_2$ could be a useful additive for this purpose and chose it for systematic studies. Indeed, we observed that the utilization of $BF_3{\cdot}OEt_2$ as an additive resulted in diminishing formation of allenyl aldol adduct **2** and increasing formation of the 3-

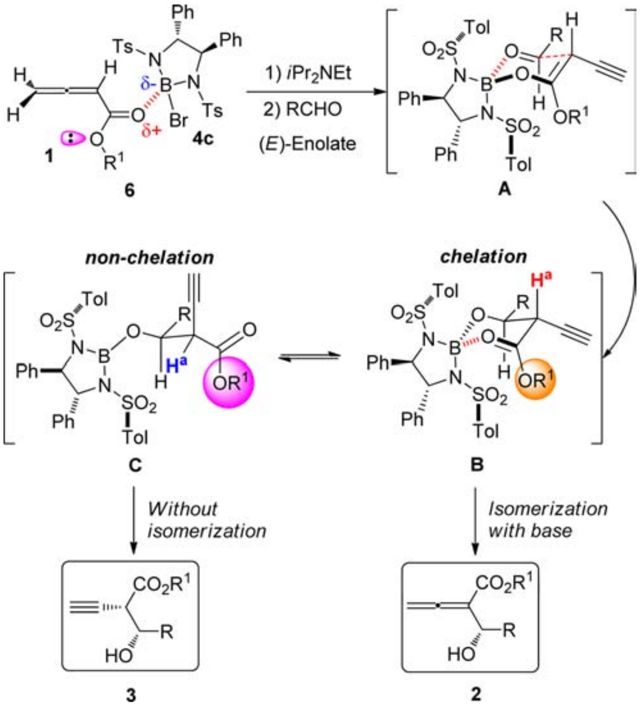
### Table 2. Optimization for the Conversion of 1 to *threo*-3[a]



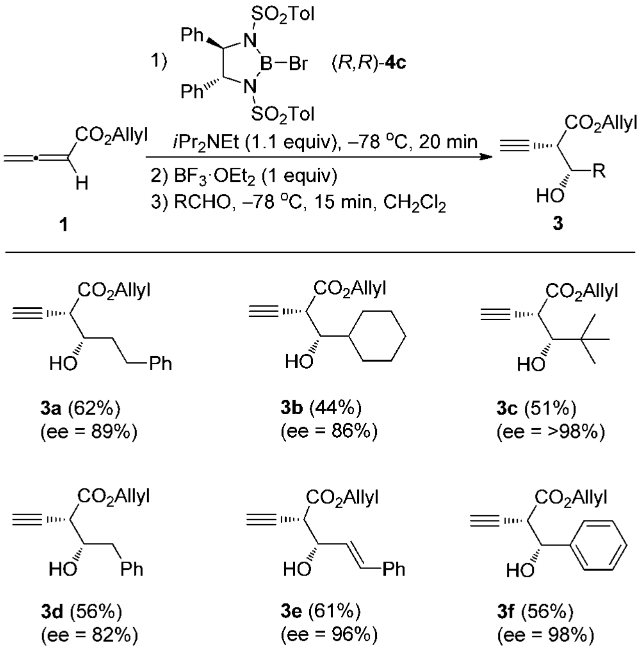
| entry | $R^1$ | base equiv | $BF_3{\cdot}OEt_2$ equiv | $t_2$[b] | 2/3/5[c] | yield[d] (%) | ee[e] (%) |
|---|---|---|---|---|---|---|---|
| 1 | Me | 2.0 | none | 2 h | 2 only | 78 | 92[f] |
| 2 | Et | 1.0 | none | 10 min | 71:21:8 | 36 | |
| 3 | Et | 1.5 | 0.5 | 20 min | 21:70:9 | 44 | |
| 4 | Pr | 1.2 | 0.5 | 20 min | 20:75:5 | 38 | 81 |
| 5 | Ph | 1.2 | 0.5 | 20 min | 14:86:0 | 37 | 61 |
| 6 | Ph | 1.5 | 1.0 | 30 min | 10:90:0 | 41 | 64 |
| 7 | *t*Bu | 1.2 | 0.5 | 20 min | 3 only | 63 | 52 |
| 8 | *t*Bu | 1.2 | 1.0 | 30 min | 3 only | 78 | 54 |
| 9 | allyl | 1.2 | 1.0 | 15 min | 3 only | 62 | 89 |

[a] Reactions were carried out in $CH_2Cl_2$. [b] Reaction time. [c] Determined by $^1H$ NMR of crude products. [d] Isolated yields. [e] Determined by HPLC analysis of the benzoylated diol **8a**. [f] Enatiomeric excess value of **2a**.

### Scheme 3. Chemical Pathways for 2 and 3 from 1



### Scheme 4. Allenoate Aldol Reaction of 1 ($R^1$ = Allyl) to 3[a]



[a] Same conditions outlined in Table 2.

butynoate aldol adduct **3** (Table 2, entries 3–6). However, the problem with the formation of **2** and low chemical yields needed to be solved.

To find optimal conditions, a series of experiments was performed with various allenoates **1**. Reaction of **1** ($R^1$ = *t*-butyl) under similar conditions ($t_2$, 30 min) indicated that the exclusive conversion to the corresponding *threo*-**3** ($R^1$ = *t*-butyl) was achieved in 78% yield. However, the enantioselectivity turned out to be lower (ee = 54%) than other cases (Table 2, entry 8). We observed that allyl allenoate **1** ($R^1$ = allyl) could be a suitable substrate to provide **3** in 62% yield with 89% ee (Table 2, entry 9). Under optimal conditions, a reaction was performed by addition of $BF_3{\cdot}OEt_2$ (1.0 equiv) followed by hydrocinnamaldehyde (2 equiv) to a resulting solution of the boron enolate prepared from **1** ($R^1$ = allyl) with **4c** under the same conditions. The reaction continued for 15 min at −78 °C, and then the usual workup procedure provided **3a** as a single diastereomer. Reaction conditions were also effective for various aldehydes (Scheme 4). Note that the reaction produced neither **2** nor **5** according to the analysis of $^1H$ NMR spectra of the crude products.

The preference of *threo*-diastereoselectivity for the larger $R^1$ group in allenoate **1** can be explained by the formation of a boron (*E*)-enolate in **A** from allenoate **1** (Scheme 3). Intermediate **6**, which is the result of the complexation between the lone pair of the carbonyl oxygen of allenoate **1** and the boron of **4c**, should adopt the conformation shown in Scheme 3 due to electronic and steric reasons.[15] Subsequent enolization of complex **6** in the presence of *i*$Pr_2NEt$ to (*E*)-enolate and then addition to aldehyde via a chairlike intermediate **A** provides **B** and **C**. We observed that isomerization from 3-butynoate **B** to allenoate **2** during reaction is favored by a smaller $R^1$ over a larger $R^1$. This phenomenon can be accounted for by analysis of possible intermediates **B** and **C** in Scheme 3. For the isomerization to occur from 3-butynyl to the allenyl moiety, $H^a$ in **B** and **C** must be acidic enough. Formation of the allenyl aldol adduct **2** via intermediate **B** can be explained by assuming that the tight coordination of the ester moiety to the boronyl moiety provides a geometrical validity of $H^a$ with the carbonyl group to satisfy the isomerization with base from **B** to **2**. On the other hand, formation of *threo*-**3** must result from a nonchelation intermediate **C** due to a steric repulsion between the larger $R^1$ group in ester and the *N*-sulfonamidyl group.

To verify the stereochemistry in products **2** and **3**, we carried out the synthesis of several compounds to compare their spectroscopic and optical data with known compounds (Scheme 5). Cyclocarbonylation of **2d** with $Ru_3(CO)_{12}$ (2 mol %) in the presence of $Et_3N$ under CO atmosphere (15 atm) at 90 °C in dioxane resulted in the formation of lactone **7** in 44% yield,[16] a methyl ester of striatisporolide A.[17] Although the absolute configuration of **7** was deduced by comparison of specific

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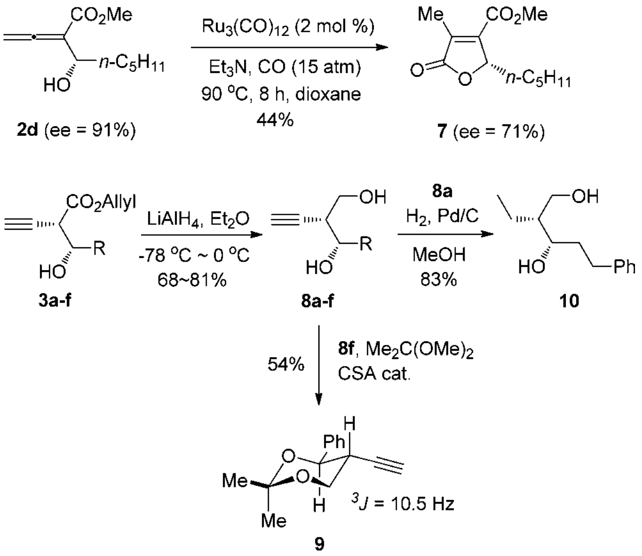
**Scheme 5. Chemical Transformations of 2 and 3 To Prove Their Stereochemistry**



rotation with literature values,[18] optical purity of **7** was diminished to 71% ee starting from 91% ee (**4d**), presumably due to a partial epimerization under harsh reaction conditions. Diols **8a−f** were cleanly prepared by $LiAlH_4$ reduction of **3a−f** in good yields. The stereochemical assignment for *threo*-**3** was based on the magnitude of the vicinal coupling constant of six-membered ring protons in the 1,3-dioxane **9** obtained from **8f**. Conversion of **8a** to **10** was achieved by catalytic hydrogenation on Pd/C in MeOH in 83% yield. Finally, relative and absolute configurations of **10** were proven by comparison of NMR and specific rotation to the literature.[19]

In summary, this paper describes highly selective synthetic routes to allenoate **2** and *threo*-3-butynoate **3** from an aldol reaction of allenoate **1** with aldehydes in a general and efficient way that promises to be synthetically useful. We observed that Lewis acid additive $BF_3{\cdot}OEt_2$ plays a crucial role in the formation of **3** to prevent an isomerization by scavenging excess amine base. Studies are in progress for the extension of methods to other aldol routes, especially the $\gamma$-addition process, and their applications to natural product synthesis.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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