

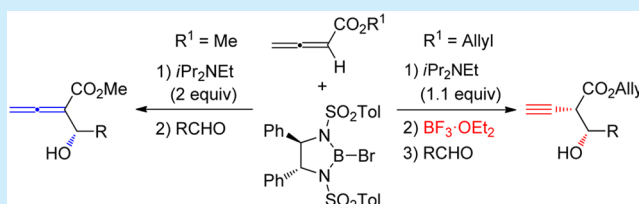
Asymmetric Aldol Reaction of Allenates: Regulation for the Selective Formation of Isomeric Allenyl or Alkynyl Aldol Adduct

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S Supporting Information

ABSTRACT: A highly stereoselective synthesis of 3-butynyl-*threo*-aldol adducts is achieved from the reaction of allyl allenate with a chiral bromoborane in the presence of *i*Pr₂NEt, followed by addition of BF₃·OEt₂ 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 allenate.



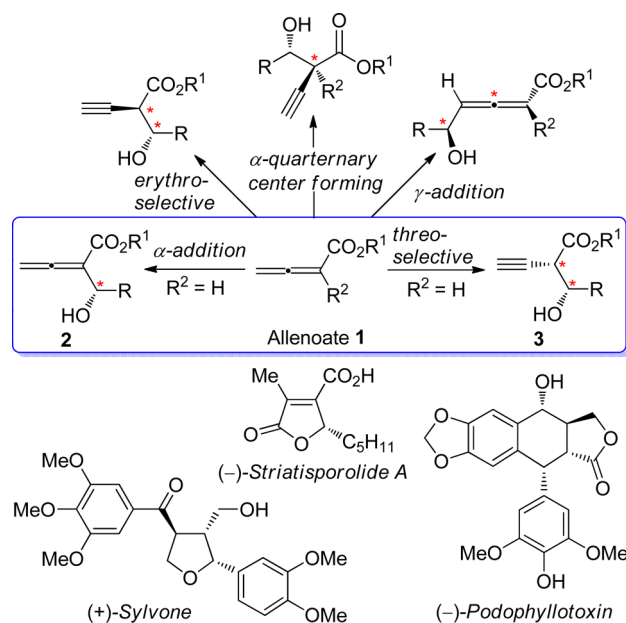
The discovery of efficient asymmetric methods to achieve the synthesis of enantiomerically pure compounds is of considerable interest in organic chemistry.¹ In light of widespread advances in asymmetric methods, aldol reactions of carbonyl functionalities using chiral auxiliaries or catalysts led to significant developments in the area of asymmetric synthesis.² Numerous successful methodologies using stoichiometric amounts of chiral reagents³ and catalytic amounts of chiral Lewis acids,⁴ bases,⁵ and organocatalysts⁶ 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 asymmetric routes using allenyl substrates. In this regard, we became quite interested in exploring stereo- and regioselective aldol routes starting from allenate **1** to a variety of products possessing versatile functional groups (Scheme 1).⁸

Allenates 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 allenates 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 allenate **1** with aldehydes, which allows reactions in good yields with high levels of stereo-selectivity (Scheme 1). To the best of our knowledge, there has been no report of stereoselective synthesis of aldol adducts such

Scheme 1. Design of Allenate Aldol Routes and Targets



as allenyl **2** and 3-butynyl **3** from allenate **1**.¹¹ Furthermore, synthetic applications can be foreseen for the products to give a variety of bioactive substances (Scheme 1).

The first study focusing on the use of allenates **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 Ipc₂BX (**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*Pr₂NEt 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 allenolate 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*Pr₂NEt at $-78\text{ }^{\circ}\text{C}$ for 1 h, followed by treatment with hydrocinnamaldehyde at $-78\text{ }^{\circ}\text{C}$ 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>i</i> Pr ₂ NEt	1	CH ₂ Cl ₂		
2	4b	Me	<i>i</i> Pr ₂ NEt	1	CH ₂ Cl ₂		
3	4c	Me	<i>i</i> Pr ₂ NEt	1	CH ₂ Cl ₂	40	90
4	4c	Me	Et ₃ N	1	CH ₂ Cl ₂	21	
5	4c	Et	<i>i</i> Pr ₂ NEt	1	CH ₂ Cl ₂	47	88
6	4c	Me	<i>i</i> Pr ₂ NEt	1	toluene	23	84
7	4c	Me	<i>i</i> Pr ₂ NEt	0.3	CH ₂ Cl ₂	78	92

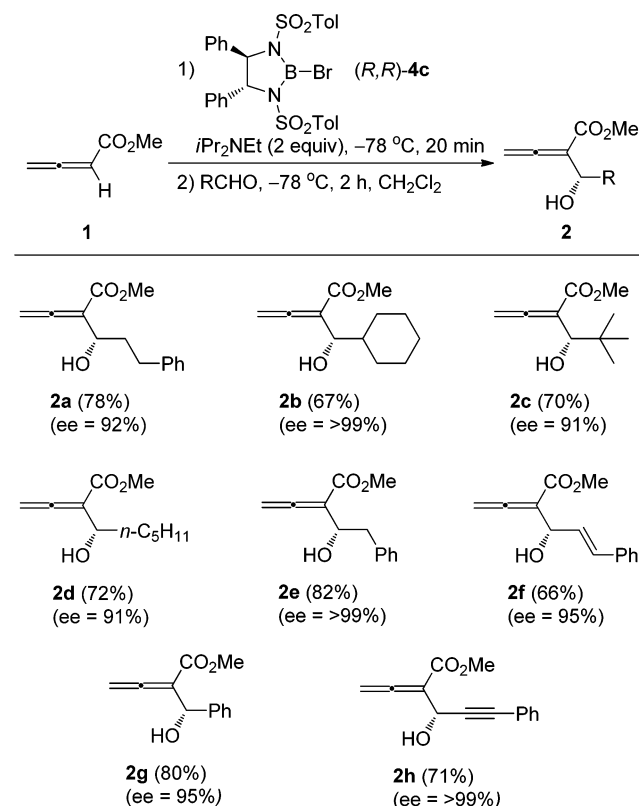
^aUsing 2 equiv. ^bEnolization time. ^cYields are those of products isolated after purification by chromatography. ^dDetermined by analysis of HPLC.

During optimization studies, several key findings emerged (entry 7): (1) about 20 min of the enolization time at $-78\text{ }^{\circ}\text{C}$ resulted in the best chemical yields; (2) *i*Pr₂NEt (2 equiv) proved to be a suitable base compared to other bases such as Et₃N and *N*-methylpyrrolidine for this transformation; (3) reactions performed in CH₂Cl₂ resulted in the best chemical yields in comparison with other solvent systems including toluene; (4) methyl allenolate is superior to ethyl allenolate 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** (R¹ = Me) with hydrocinnamaldehyde in CH₂Cl₂ 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.

In an effort to expand the scope of chemical transformation in the synthesis of **2** from allenolate **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

Scheme 2. Allenolate Aldol Reaction of **1** (R¹ = Me) to **2**^a

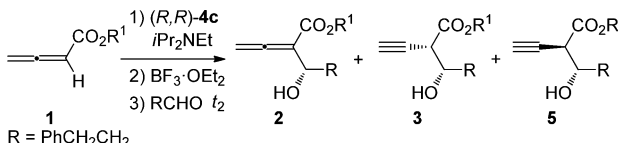


^aFor conditions, see Table 1.

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*Pr₂NEt between allenolate **1** and the aldehyde, which produces 3-butenyl aldol adduct **3**. The second step of the reaction would be the isomerization of alkyne **3** to allenolate **2**. In general, the isomerization from **3** to more stable α,β -unsaturated allenolate **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-butenyl 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*Pr₂NEt because the isomerization was attributed to the use of excess base during the reaction. Initial attempts for reaction of **1** (R¹ = Et) with **4c** in the presence of *i*Pr₂NEt (1 equiv) under the same conditions and then with hydrocinnamaldehyde for 10 min at $-78\text{ }^{\circ}\text{C}$ indicated that the conversion to the desired 3-butenyl adducts **3** and **5** turned out to be only marginal. Reaction always produced **2** (R¹ = Et) as a major component along with the 3-butenyl 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 BF₃·OEt₂, B(OMe)₃, and Al(OEt)₃, we found that BF₃·OEt₂ could be a useful additive for this purpose and chose it for systematic studies. Indeed, we observed that the utilization of BF₃·OEt₂ 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 ·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	<i>t</i> Bu	1.2	0.5	20 min	3 only	63	52
8	<i>t</i> Bu	1.2	1.0	30 min	3 only	78	54
9	allyl	1.2	1.0	15 min	3 only	62	89

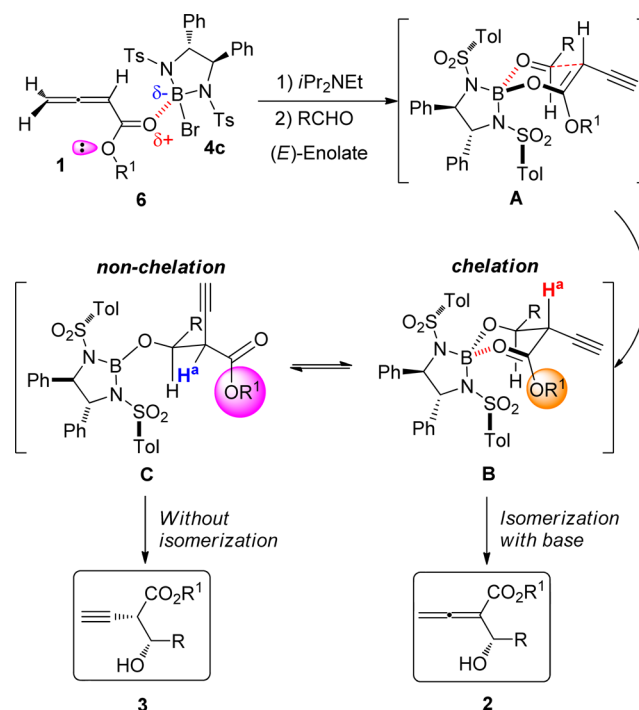
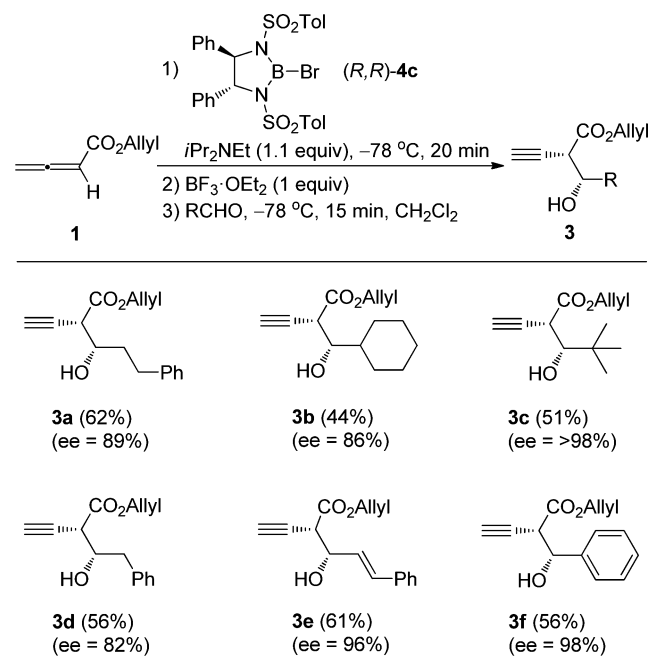
^aReactions were carried out in CH₂Cl₂. ^bReaction time. ^cDetermined by ¹H NMR of crude products. ^dIsolated yields. ^eDetermined by HPLC analysis of the benzoylated diol 8a. ^fEnantiomeric excess value of 2a.

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 allenolates 1. Reaction of 1 (R¹ = *t*-butyl) under similar conditions (t₂, 30 min) indicated that the exclusive conversion to the corresponding *threo*-3 (R¹ = *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 allenolate 1 (R¹ = 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 BF₃·OEt₂ (1.0 equiv) followed by hydrocinnamaldehyde (2 equiv) to a resulting solution of the boron enolate prepared from 1 (R¹ = 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 R¹ group in allenolate 1 can be explained by the formation of a boron (*E*)-enolate in A from allenolate 1 (Scheme 3). Intermediate 6, which is the result of the complexation between the lone pair of the carbonyl oxygen of allenolate 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*Pr₂NEt to (*E*)-enolate and then addition to aldehyde via a chairlike intermediate A provides B and C. We observed that isomerization from 3-butyrate B to allenolate 2 during reaction is favored by a smaller R¹ over a larger R¹. This phenomenon can be accounted for by analysis of possible intermediates B and C in Scheme 3. For the isomerization to occur from 3-butyrate 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

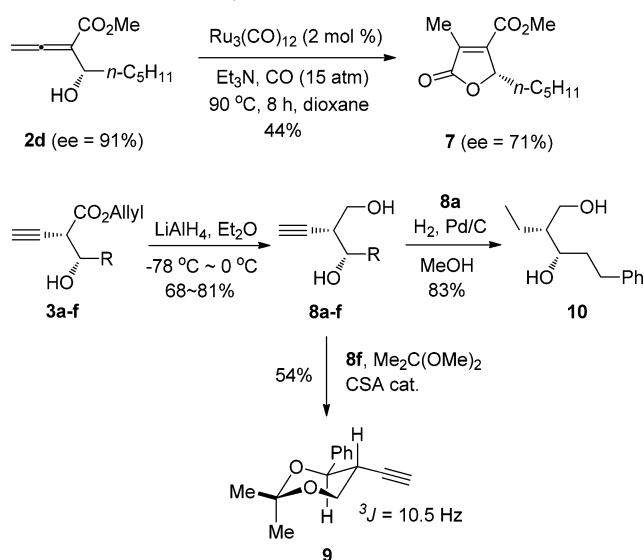
Scheme 3. Chemical Pathways for 2 and 3 from 1

Scheme 4. Allenolate Aldol Reaction of 1 (R¹ = Allyl) to 3^a

^aSame conditions outlined in Table 2.

nonchelation intermediate C due to a steric repulsion between the larger R¹ group in ester and the *N*-sulfonylamidyl 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 Ru₃(CO)₁₂ (2 mol %) in the presence of Et₃N 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

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 allenolate **2** and *threo*-3-butynoate **3** from an aldol reaction of allenolate **1** with aldehydes in a general and efficient way that promises to be synthetically useful. We observed that Lewis acid additive $\text{BF}_3 \cdot \text{OEt}_2$ 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 γ -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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