Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

A Regulation of Regiodivergent Routes for Enantioselective Aldol Addition of 2-Alkyl Allenoates with Aldehydes: α-Addition versus γ-Addition

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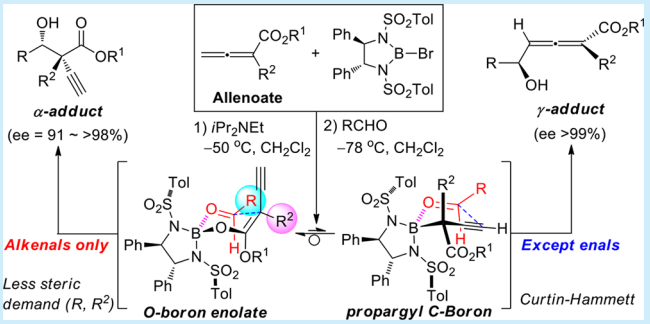
Supporting Information

ABSTRACT: A method for the regioselective asymmetric aldol addition of 2-alkyl allenoates with aldehydes to provide an α- or γ-adduct depending on the aldehyde pair is reported. In most cases, except enals, a mixture of a chiral bromoborane with 2-alkyl allenoates in the presence of iPr$_2$NEt can react with aldehydes to provide efficient γ-addition products as single isomers containing axial and central chirality. On the other hand, observations indicate that enals undergo α-addition to yield highly functionalized adducts, including an α-carbon quaternary center in high levels of diastereo- and enantioselectivity.



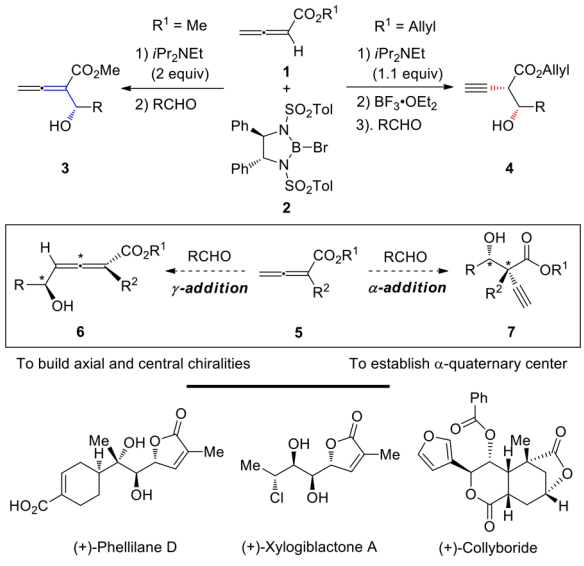
The discovery of efficient asymmetric methods to achieve the synthesis of isomerically pure compounds is of considerable interest in organic chemistry.[1] In this regard, control of regiochemical pathway is one of the most essential elements of their synthetic values.

During the course of our research program aimed at developing new synthetic methods utilizing allenyl functionalities,[2] we recently disclosed our discovery of control elements for the asymmetric aldol reaction of allenoates **1** with aldehydes to regulate selective formation of isomeric allenyl **3** or 3-butynyl aldol adducts **4**, which allows reactions in good yields with high levels of stereoselectivities.[3] With these precedents in hand, we became interested in the more challenging task of designing a regioselective aldol addition of 2-alkyl allenoates **5** to afford a γ-adduct **6** to construct an axial and central chirality at the same time, or an α-adduct **7** containing an α-carbon quaternary center (Scheme 1).

The enantioselective construction of a quaternary carbon center substituted with four distinct carbon groups is regarded as one of the important synthetic challenges.[4] Even though there have been several elegant reports for the construction of cyclic quaternary carbon stereogenic centers, only few methods can yield such sterochemical features in an acyclic system.[5]

The lack of data in the literature concerning direct addition of an enolate to carbonyl units via an aldol-type reaction surprised us, especially with respect to the expected similarity of such system to the well-defined allylation reactions.[6] Only notable methods have been demonstrated by the Marek group[7] using Cu-enolates starting from ynamides and the Denmark group[8] using silyl ketene imines as a nucleophile.

Scheme 1. Allenoate Aldol Routes



Since the first pioneering work toward the enantioselective addition of allenoates to imines by the Miller group, several Mannich-type reactions have been reported.[9] Subsequent to early studies on the allenoate aldol reaction to carbonyl functionalities by Hammond,[10] two research groups have made important contributions to the steady improvement in this

Received: January 23, 2018

DOI: 10.1021/acs.orglett.8b00219
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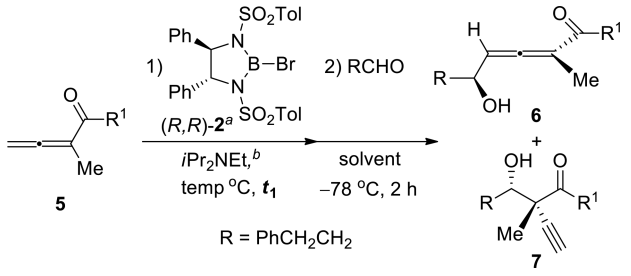
methodology for enantioselective versions of a γ-addition.[11,12] Nonetheless, each of the known methods has included some limits of utilization, such as restriction of substrates and/or carbonyl electrophiles.

Herein, we report control factors for a general and efficient method of the allenoate aldol reaction from **5** to regulate the regiochemical routes to γ-addition product **6** and α-addition product **7** with high levels of regio- and stereoselectivity. In addition, synthetic applications can be foreseen for the products to give a variety of bioactive natural products (Scheme 1).

With this issue in mind, our investigations began with various allenoates **5**, as shown in Table 1 to judge feasibility as a substrate. Attempts to perform an aldol reaction with **5a** (R = O*t*-Bu) under previously employed conditions ((1) **2**, *i*Pr$_2$NEt (2 equiv), −78 °C, CH_2Cl_2, 1 h; (2) $PhCH_2CH_2CHO$, −78 °C)[3] showed conversion to the corresponding γ-adduct **6** and/or α-adduct **7** could not be satisfied at −78 °C. We could not also observe any notable reaction progress with **5b** (R = OEt) under the same conditions (Table 1, entries 1 and 2). After surveying reaction conditions, we found that the enolization temperature (temp °C) and time (t_1) were crucial factors for optimal conditions (Table 1, entries 3−5). Initial experiments on the enolization of **5a** with **2** in the presence *i*Pr$_2$NEt at −50 °C for 1 h, followed by treatment with hydrocinnamaldehyde at −78 °C for 2 h, produced **6a** as a sole adduct instead of **7** (Table 1, entry 3). We were surprised to observe the formation of the γ-adduct **6** only via our allenoate aldol reaction. To the best of our knowledge, a conjugated γ-addition of the corresponding boron enolate with a carbonyl functionality has not been reported in the literature.[13]

Table 1. Selected Preliminary Investigations[a]



entry	5	R^1	temp °C, t_1[c]	solvent	products	yield[d]	ee, %[e]
1	**5a**	O*t*-Bu	−78 °C, 1 h	CH_2Cl_2	NR	–	–
2	**5b**	OEt	−78 °C, 1 h	CH_2Cl_2	NR	–	–
3	**5a**	O*t*-Bu	−50 °C, 1 h	CH_2Cl_2	**6a**	58	>99
4	**5a**	O*t*-Bu	−50 °C, 0.5 h	CH_2Cl_2	**6a**	77	>99
5	**5a**	O*t*-Bu	−60 °C, 0.5 h	CH_2Cl_2	**6a**	62	>99
6	**5b**	OEt	−50 °C, 0.5 h	CH_2Cl_2	**6g**	63	>99
7	**5a**	O*t*-Bu	−50 °C, 0.5 h	toluene	**6a**	<5	NA
8	**5a**	O*t*-Bu	−50 °C, 0.5 h	EtCN	NR	–	–
9	**5c**	OPh	−50 °C, 0.5 h	CH_2Cl_2	NR	–	–
10	**5d**	S*t*-Bu	−50 °C, 0.5 h	CH_2Cl_2	NR	–	–
11	**5e**	SPh	−50 °C, 0.5 h	CH_2Cl_2	NR	–	–

[a]0.95 equiv. [b]2 equiv. [c]Enolization time. [d]Isolated yield (%) after purification by flash chromatography. [e]Enantiomeric excess (%) values were determined by HPLC analysis.

During optimization studies, several key findings emerged: (1) an ∼30 min enolization time at −50 °C resulted in the best chemical yields (Table 1, entry 4); (2) reactions performed in CH_2Cl_2 resulted in the best chemical yields in comparison with other solvents, including toluene and EtCN (Table 1, entries 7, 8); (3) *tert*-butyl and ethyl allenoates (**5a**,**b**) are superior to others in terms of chemical yield and enantioselectivity and were chosen for the systematic studies (Table 1, entries 9−11); (4) reactions exclusively produced γ-addition adduct **6** as the sole product; (5) absolute and relative stereochemistry are confirmed by X-ray crystallography of the corresponding **6g**-carbamate (CCDC 1551393) prepared from **6g** and (*S*)-(−)-1-phenylethyl isocyanate (see the Supporting Information (SI) for details).

With the notion that this approach might lead to a general and efficient method for the synthesis of γ-adduct **6**, we set out to explore different aldehydes with **5** (R^1 = *t*-Bu, Et; R^2 = Me, Et) to extend the reaction scope. Indeed, the method turned out to be successful with structurally diverse aldehydes (1°, 2°, 3°, and Ph) forming exclusively γ-addition aldol products **6** in moderate to good yields, except in the case of benzaldehyde (formed <5% of α-adducts, dr = 9:1). It is worth noting that the reaction produced γ-adducts in diastereo- and enantiomerically enriched form for all cases with >99% ee based on HPLC analysis as it can be seen in Scheme 2.

In an effort to expand the scope of our allenoate aldol reaction, we next focused on the utilization of α,β-unsaturated aldehydes (Scheme 3).

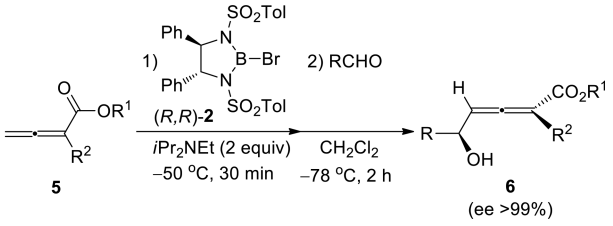
Reaction of 3-phenyl-2-propynal, an alkynal, with **5a** under the same conditions appeared in Scheme 2 provided the γ-adduct **6t** in 38% yield as a somewhat unstable form, whereas cinnamaldehyde, an alkenal, afforded the γ-adduct **6s** along with substantial amounts of the α-adduct **7a** in a ratio of 2:1 in 48% yield. Enantioselectivities for both products turned out to be excellent (**6s** and **6t**, ee >99%; **7a**, ee = 96% based on HPLC analysis). The structure of **7a** was unambiguously established by X-ray crystallography (CCDC 1551394). Additionally, *tert*-butyl 2-methylallenoate **5a** was revealed to be much more effective than **5b** for the formation of **7**.

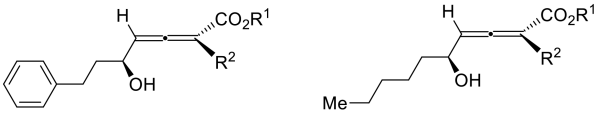
We speculated that the formation of an α-adduct from cinnamaldehyde could allow us to evaluate the nature of the allenoate aldol reaction, and also might lead to a general method for α-addition to construct an α-quaternary center. Subsequently, the remarkable observation has been made that the introduction of (*E*)-crotonaldehyde as an electrophile under the same conditions resulted in the formation of the α-adduct **7b** as a single diastereomer with >98% ee in 78% yield (Scheme 4). Indeed, we observed that the use of various enals led to diastereospecific α-addition in good yields with high levels of enantioselectivity as shown in Scheme 4.

From the mechanistic perspective, two major functions for the reaction routes of allenoate aldol process are immediately discernible: formation of boron (*E*)-enolate **8** and interconversion of *O*-boron enolate **8** and propargylic *C*-borane **9**.[14] Scheme 5 illustrates possible stereochemical routes for α-adduct **7** and γ-adduct **6**. We propose addition of boron (*E*)-enolate **8** to aldehyde to go through a chairlike stereochemical model **A** to provide the α-adduct **7**. On the other hand, we propose that γ-adduct might be obtained from propargylic *C*-borane **9** through a propargylboration **B**.

DOI: 10.1021/acs.orglett.8b00219
Org. Lett. XXXX, XXX, XXX−XXX

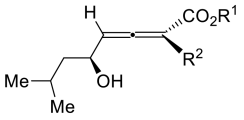
Scheme 2. γ-Addition of Allenoate Aldol Reaction of 5[a,b,c]



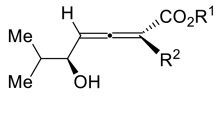


6a, R^1 = *t*-Bu, R^2 = Me (77%)
6g, R^1 = Et, R^2 = Me (63%)
6m, R^1 = *t*-Bu, R^2 = Et (81%)

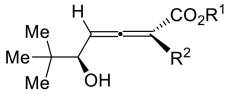
6b, R^1 = *t*-Bu, R^2 = Me (71%)
6h, R^1 = Et, R^2 = Me (67%)
6n, R^1 = *t*-Bu, R^2 = Et (68%)



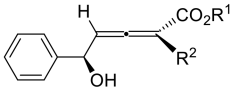
6c, R^1 = *t*-Bu, R^2 = Me (75%)
6i, R^1 = Et, R^2 = Me (68%)
6o, R^1 = *t*-Bu, R^2 = Et (71%)



6d, R^1 = *t*-Bu, R^2 = Me (67%)
6j, R^1 = Et, R^2 = Me (51%)
6p, R^1 = *t*-Bu, R^2 = Et (71%)



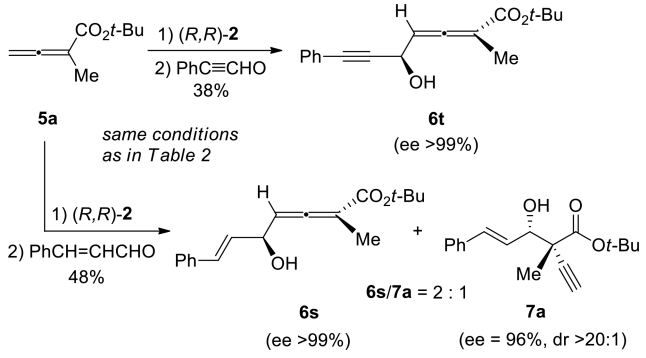
6e, R^1 = *t*-Bu, R^2 = Me (63%)
6k, R^1 = Et, R^2 = Me (53%)
6q, R^1 = *t*-Bu, R^2 = Et (67%)



6f, R^1 = *t*-Bu, R^2 = Me (62%)[d]
6l, R^1 = Et, R^2 = Me (57%)
6r, R^1 = *t*-Bu, R^2 = Et (71%)

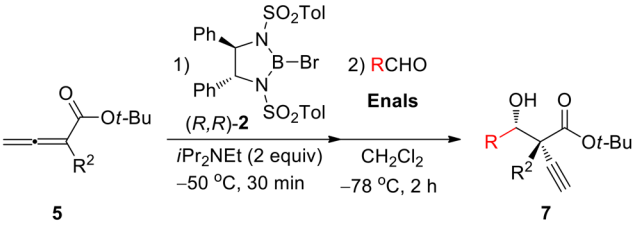
[a]See SI for experimental details. [b]Enantiomeric excess (%) values were determined by HPLC analysis in comparison with corresponding enantiomers prepared from (*S*,*S*)-**2**. [c]Isolated yields (%) after purification by flash chromatography. [d]Produced α-adducts as minor products (<5% yield, dr = 9:1).

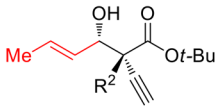
Scheme 3. Allenoate Aldol Reaction of α,β-Unsaturated Aldehydes



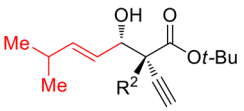
While we can use our model to rationalize the stereochemical outcomes, other important questions remained to be resolved. "What is the control factor for the formation of α-adduct or γ-adduct?" In an attempt to answer this question, we tried to isolate possible intermediates under the exact same reaction conditions. After the enolization of allenoate **5** with **2** in the presence of iPr$_2$NEt at −50 °C for 30 min in CH_2Cl_2, an oxidant[15] such as $NaBO_3$, H_2O_2/NaOH, or oxone was added to

Scheme 4. α-Addition of Allenoates 5 with Enals[a,b,c]

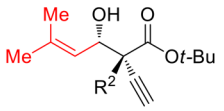




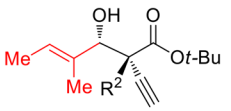
7b, R^2 = Me (78%, ee >98%)
7f, R^2 = Et (71%, ee = 93%)



7c, R^2 = Me (68%, ee = 95%)
7g, R^2 = Et (75%, ee = 92%)



7d, R^2 = Me (63%, ee = 94%)
7h, R^2 = Et (57%, ee = 96%)



7e, R^2 = Me (67%, ee = 95%)
7i, R^2 = Et (74%, ee = 91%)

[a]See SI for experimental details. [b]Enantiomeric excess (%) values were determined by analysis of 500 MHz ^{1}H NMR of (*R*)-MTPA esters in comparison with corresponding diasteromers of (*R*)-MTPA esters prepared from (*S*,*S*)-**2**. [c]Isolated yields (%) after purification by flash chromatography.

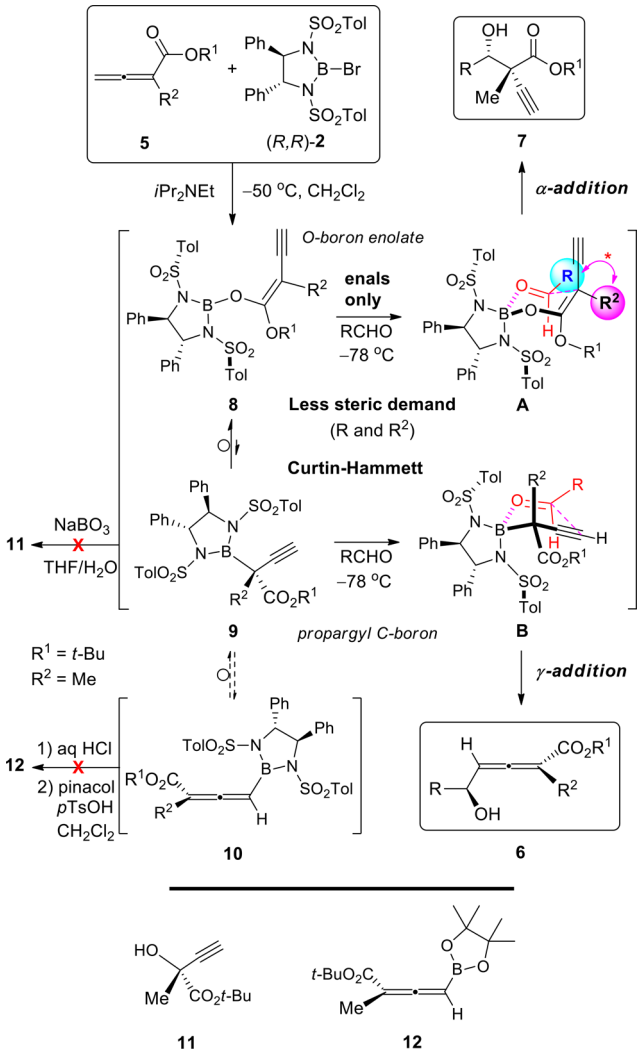
isolate **11**, which may prove a stereospecific rearrangement or not. However, **11** was not formed under various conditions, and starting allenoate **5** was recovered in up to 70% yield. Attempts to convert unstable diazaborolidines **8** and **9** to an isolable boronate **12** by the Hoppe method[16] were unsuccessful. Based on our experiments and observations, the O-boron enolate **8** exists as the predominant major isomer in equilibrium with propargylic C-boron **9** prior to aldehyde addition. Therefore, α-addition occurs in a chairlike transition state **A** with less steric demanding alkenals due to a repulsion between R and R^2 to form **7**. The γ-addition pathway could be dependent on the stability in the transition state under kinetic control such as orientations and steric factors without a necessary link to stabilities of products and equilibrium of boron reagents (the Curtin−Hammett principle). Thus, we believe that the origin of the regiochemical outcomes for **6** via γ-addition might be a subtle geometrical preference for orientation in the model **B**.

The γ-adduct **6** is readily amenable for further conversion to useful synthetic intermediates including γ-butenolides[17] by the functional group transformations.

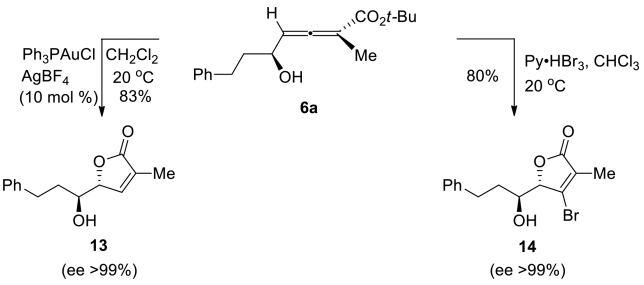
For this purpose we decided to undertake synthesis of 3-methylfuran-2(5*H*)-ones **13**[18] via gold catalysis[19] and **14** via bromination,[20] not only to show synthetic applicability for both isomers but also to apply for the synthesis of (+)-xylogiblactone A and (+)-phellilane D (Scheme 1). We reasoned that if an olefin group has more affinity to electrophiles than conjugated olefin in allenyl moiety, it might be possible to cyclize by a less reactive ester functionality to furnish a lactone. Reaction of **6a** with $Ph_3PAuCl/AgBF_4$ (10 mol %) at 20 °C in CH_2Cl_2 afforded **13** in 83% yield (Scheme 6). Bromination of **6a** with Py·HBr_3 at 20 °C in $CHCl_3$ afforded **14** in 80% yield.

DOI: 10.1021/acs.orglett.8b00219
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Stereochemical Pathways for 6 and 7



Scheme 6. Oxacyclizations of 6a to γ-Butenolides



In summary, we describe a highly selective synthetic route to γ-adducts **6** and α-adducts **7** from an aldol reaction of allenoates **5** with aldehydes. We demonstrate this reaction is general for a variety of aldehydes, and an efficient method that promises to be synthetically useful. We observed that the nature of aldehydes plays a crucial role in the regiochemical outcomes for selecting reaction routes. Studies are in progress for the extension of methods to other allenoate aldol routes and their applications to natural product syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00219.

Detailed experimental procedures and full spectroscopic and HPLC data for all new compounds (PDF)

Accession Codes

CCDC 1551393−1551394 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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§J.B. and C.O. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Research Foundation (NRF), Korea for supporting this work (C.M.Y., 2015R1D1A1-A01060430; J.K., 2015R1C1A1A02037010 and 2015R1A4A-1041036).

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DOI: 10.1021/acs.orglett.8b00219
Org. Lett. XXXX, XXX, XXX−XXX