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Allenoate Prenucleophiles: A Triply Diastereoselective Approach to β-Hydroxy Esters Containing All-Carbon α-Quaternary Centers

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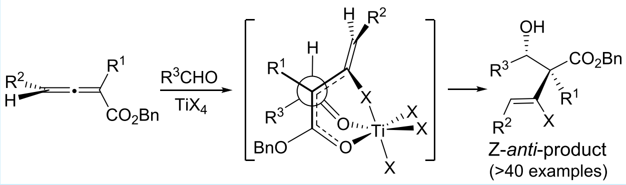
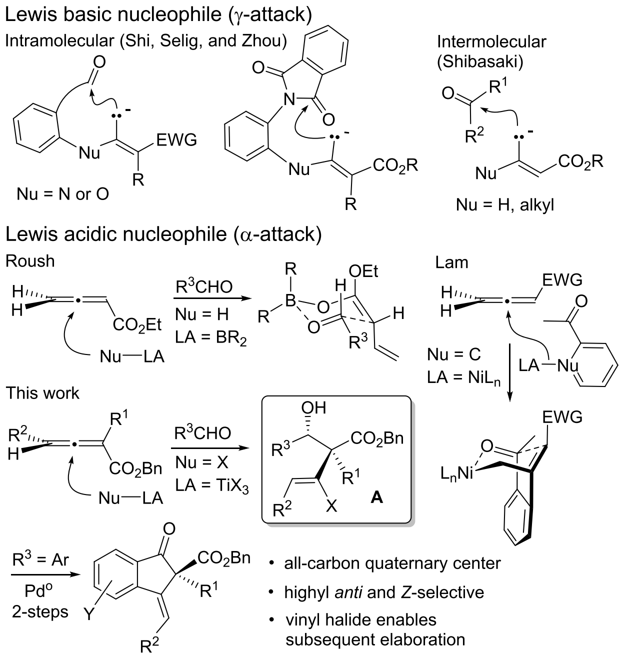
Supporting Information

ABSTRACT: Allenyl esters activated by titanium(IV) underwent additions to a wide range of aldehydes in high regio- and diastereoselectivities leading to products containing an all-carbon quaternary center bearing an α-vinyl group that was installed with high selectivity for the *Z*-geometry. An aldol product was also converted to an indanone offering a new route to this important compound class. Product triple diastereoselectivity has been rationalized using a concerted transition-state model.



There is a continuing need for tools to construct highly substituted acyclic carbon centers,[1] in part due to their growing prevalence in the structures of medicinally valuable compounds.[2] In this regard, allenoates have been exploited as useful building blocks under the action of Lewis acid catalysts[3] or Lewis base catalysts,[4] including our own work involving alkoxide- and fluoride-promoted reactions.[5] Allenoates have also served as prenucleophiles[6] in addition reactions to carbonyl electrophiles in the presence of stoichiometric activating agents. For example, Shi,[7] Selig,[8] and most recently, Zhou[9] demonstrated that, under Lewis basic conditions, heteroatom attack of the allenoate sp carbon led to anion formation followed by subsequent exclusive addition to the γ-carbon leading to cyclic products (Figure 1). Shibasaki[6] demonstrated that reducing and nucleophilic alkylating reagents in a Lewis basic regime also convert allenoates to nucleophiles that undergo intermolecular γ-additions.

Under Lewis acidic conditions, a nucleophile and its carbonyl target can in theory be tethered by a chelating metal to promote α-selective additions; however, only a few such examples exist. Lam used a Ni catalyst to facilitate aryl attack of an allenoate followed by its intramolecular α-addition to a carbonyl (Figure 1).[10] An analogous intermolecular approach was taken by Roush, who activated an allenoate through reduction with a chiral stoichiometric borane reagent. Subsequent α-addition to aldehyde was thought to occur by a boron-chelated six-membered ring transition state.[11] In seeking alternatives to chiral boron reagents to produce congested aldol products, we noted the work of Lu, who created α-vinyl-β-hydroxy ketones using allenyl ketones and zirconium(IV) chloride, though diastereoselectivities were poor for most substrates.[12] We reasoned that other Lewis acidic reagents may be more successful in bringing about an ordered bimolecular addition of allenoates and aldehydes or ketones. In the present communication, we describe how allenyl ester prenucleophiles activated by Ti(IV) reagents led to hydroxy esters **A** as single diastereomer products bearing an α-quaternary center. While a variety of multistep strategies such as the Ireland−Claisen[13] and radical cyclization[14] lead to similar congested products, to our knowledge, the present halo-aldol reaction is the first



- all-carbon quaternary center
- highyl *anti* and *Z*-selective
- vinyl halide enables subsequent elaboration

Figure 1. Activation strategies for allenoate prenucleophiles.

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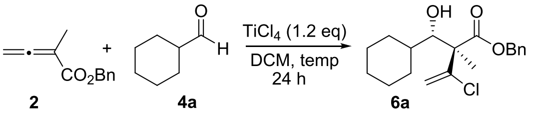
general approach[15] to accomplish this transformation in a single step. Furthermore, these aldol products are synthetically useful building blocks; here, we demonstrate their utility in accessing highly functionalized indanes.

In our initial studies involving the addition of allenoate **2** to aliphatic aldehyde **4a**, no reaction occurred at −20 °C. Warming to room temperature overnight led to significant formation of **6a** in high diastereoselectivity; however, we observed that the ester underwent debenzylation at this temperature leading to diminished yields (Table 1, entry 1).

Table 1. Optimization Study



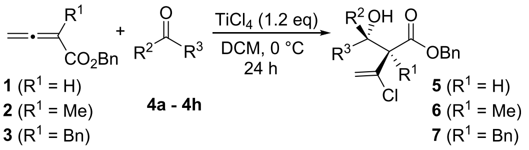
entry	temp (°C)	Lewis acid (equiv)	% yield[a]	dr[b]
1	−20 to rt	1.2 (1 M)	50	>20:1
2	0	1.2 (1 M)	88[c]	>20:1
3	rt	1.2 (1 M)	82[d]	93:7
4	0	0.3 (1 M)	20	92:8
5	0	1.2 (neat)	39	
6[e]	0	1.2 (1 M)	70	93:7

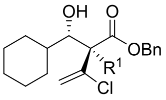
[a]Isolated yields. [b]Diastereomeric ratio determined by ^{1}H NMR of crude reaction mixture. [c]The yield was 54% after 6 h. [d]Optimal reaction time here was 6 h; longer times led to some debenzylation. [e]Normally, LA was added last in this reaction. In this case, the order of addition was allene and LA first followed by aldehyde.

Although the use of less labile esters solved this problem,[16] we sought to develop conditions for benzyl esters owing to the wide utility of this protecting group. Debenzylation side product formation was avoided by performing the reaction at 0 °C, which afforded optimal yields of **6a** provided the reaction was allowed to proceed for 24 h (entry 2). We also examined this transformation with a substoichiometric amount of titanium tetrachloride; however, the isolated yield was significantly lower than when a full equivalent (1.2 equiv) was added (entry 4). In these reactions, optimal yields were obtained by adding the Ti(IV) reagent as a dichloromethane (DCM) solution (1 M) once all other reaction components were present. Significantly lower yields were observed when neat titanium tetrachloride was added (entry 5) or when the Lewis acid was added to allene prior to aldehyde addition (entry 6). We also examined the use of tetrabutylammonium bromide as an additive (not shown in table),[17] which led to significantly diminished yields of chloride **6a** and a minimal amount of its bromo analogue (**9a**).

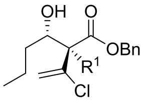
After establishing the optimal conditions, we explored the reaction scope with respect to various aldehydes (Tables 2 and 3). In general, a wide range of aldehydes react with allenes **1**−**3** to give α-chlorovinyl-β-hydroxy esters in good isolated yields. Reactions leading to products with quaternary centers (**6** and **7**) led to single diastereomers (no minor isomer detected by NMR). In contrast, addition reactions with allene **1** led to products containing a tertiary center in comparatively moderate diastereoselectivities (usually 6:1). Not surprisingly, dehydration product is observed when electron-donating aromatic aldehydes are used in the formation of product containing an α-tertiary center. This method can also be extended to additions of acetone leading to products **6d** and **7d** possessing two contiguous quaternary centers, which to our

Table 2. Reaction Scope Leading To Vinyl Chloride Products[a−c]

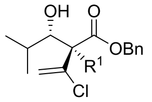




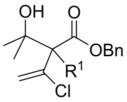
5a: 88% (>20:1 dr)
6a: 79% (>20:1 dr)
7a: 76% (>20:1 dr)



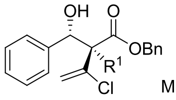
5b: 80% (76:24 dr)
6b: 96% (>20:1 dr)
7b: 79% (>20:1 dr)



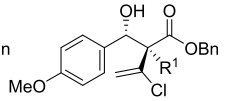
5c: 92% (86:14 dr)
6c: 85% (>20:1 dr)
7c: 65% (>20:1 dr)



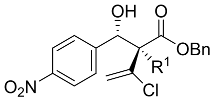
5d: 91%
6d: 79%
7d: 59%



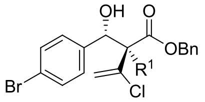
5e: 90% (90:10 dr)
6e: 72% (>20:1 dr)
7e: 61% (>20:1 dr)



5f: dehydration[d]
6f: 57% (>20:1)
7f: 41% (>20:1)



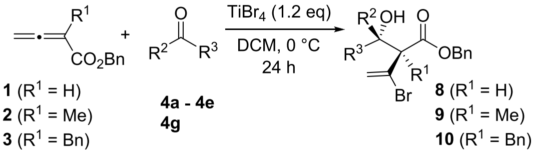
5g: 71% (78:22 dr)
6g: 67% (88:12 dr)
7g: 57% (>20:1 dr)

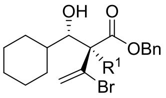


5h: 52% (88:12)
6h: 45% (>20:1)
7h: 52% (>20:1)

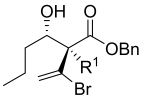
[a]Reaction conditions: **1** (1.0 equiv), **4** (0.9−0.96 equiv), TiCl$_4$ (1 M in DCM, 1.2 equiv), and DCM (0.2 M). TiCl$_4$ was added after 10 min to a mixture of allene and aldehyde. [b]Isolated yield of major diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture. [d]Underwent dehydration under the reaction conditions.

Table 3. Reaction Scope Leading To Vinyl Bromide Products[a−c]

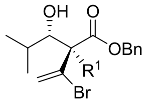




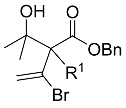
8a: 88% (87:13 dr)
9a: 79% (>20:1)
10a: 69% (>20:1)



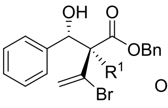
8b: 76% (86:14 dr)
9b: 81% (>20:1)
10b: 73% (>20:1)



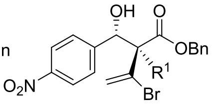
8c: 82% (88:12 dr)
9c: 81% (>20:1)
10c: 69% (>20:1)



8d: 98%
9d: 82%
10d: 31%



8e: 56% (94:6 dr)
9e: 66% (>20:1)
10e: 73% (>20:1)



8g: 60% (67:33)
9g: 71% (>20:1)
10g: 66% (>20:1)

[a]Reaction conditions: **1** (1.0 equiv), **4** (0.9−0.96 equiv), TiCl$_4$ (1 M in DCM, 1.2 equiv), and DCM (0.2 M). TiCl$_4$ was added after 10 min to a mixture of allene and aldehyde. [b]Isolated yield of major diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture. [d]Underwent dehydration under the reaction conditions.

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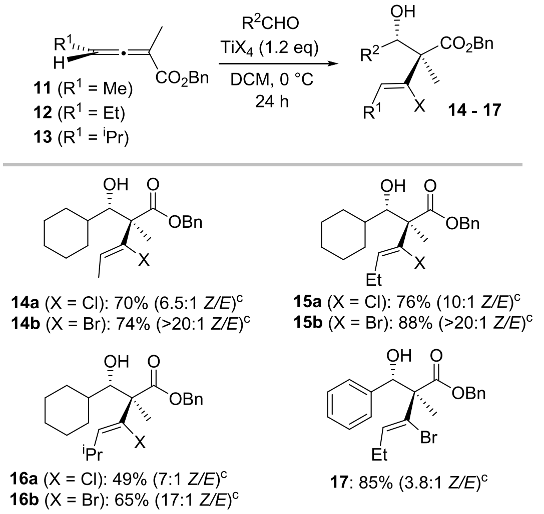
knowledge, is virtually unprecedented in acyclic systems.[18] To our surprise, titanium tetrabromide as the halogen source also efficiently led to aldol products **8**, **9**, and **10** (Table 3). Despite its greater Lewis acidity,[19] good yields and high anti-diastereoselectivity were achieved, especially with α-substituted allenoates **2** and **3**, using the same conditions as TiCl$_4$.

Perhaps more significantly, trisubstituted allenoates **11**−**13** underwent addition to cyclohexane carboxaldehyde to afford aldol products **14**−**17** bearing trisubstituted double bonds with high Z-selectivity (Table 4). Reactions mediated by TiBr$_4$ led to products with nearly complete triple diastereoselectivity. To our knowledge, there are very few reports in which acyclic products with this degree of selectivity are assembled in one step.[20] This same reaction with benzaldehyde led to compound **17** possessing complete relative anti-stereochemistry but diminished Z-selectivity.

Table 4. Addition Reactions with Trisubstituted Allenoates[a,b]



11 (R^1 = Me)
12 (R^1 = Et)
13 (R^1 = ^{i}Pr)
14 - 17

14a (X = Cl): 70% (6.5:1 Z/E)[c]
14b (X = Br): 74% (>20:1 Z/E)[c]

15a (X = Cl): 76% (10:1 Z/E)[c]
15b (X = Br): 88% (>20:1 Z/E)[c]

16a (X = Cl): 49% (7:1 Z/E)[c]
16b (X = Br): 65% (17:1 Z/E)[c]

17: 85% (3.8:1 Z/E)[c]

[a] Reaction conditions: **1** (1.0 equiv), **4** (0.9−0.96 equiv), TiBr$_4$ (1 M in DCM, 1.2 equiv), and DCM (0.2 M). TiBr$_4$ was added after 10 min to a mixture of allene and aldehyde. [b] Isolated yield of major diastereomer. [c] Diastereomeric ratio determined by ^{1}H NMR of crude reaction mixture.

To determine the relative stereochemistry of the major products resulting from these halo aldol reactions, we obtained an X-ray crystal structure of product **9g**, which indicated anti-stereochemistry (Figure 2). We were unable to crystallize a product containing an α-tertiary center and thus turned to NMR experiments to elucidate relative configuration. To this end, ester **5a** was reduced to form the corresponding diol followed by conversion to acetal **18** (Scheme 1). The ^3J coupling revealed by ^{1}H NMR was 10.3 Hz, strongly suggesting the anti conformation.

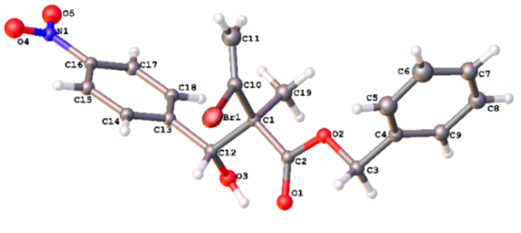
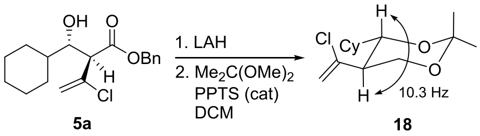


Figure 2. Crystal structure of product **9g** showing the anti configuration.

Scheme 1. Assignment of Relative Stereochemistry



5a **18**

Although we are actively investigating the mechanism for the present halo aldol reaction, our current hypothesis is that the reaction proceeds via a closed transition state, which is common for titanium(IV) enolates.[21] Others have hypothesized an open-transition-state model for similar reactions involving Al(III) reagents;[22] however, in our work, TiX$_4$ coordinates allenyl ester to deliver halide in an intramolecular fashion. Titanium coordination geometry also allows for aldehyde chelation, setting up a favorable six-membered ring transition state (Figure 3a). In this concerted model where halogenation occurs at the same time as carbon−carbon bond formation, relative stereochemistry is established by the orientation of the aldehydic substituent (R^3). To minimize steric interactions with the forming vinyl unit, we argue that the R^3 substituent orients itself closer to the ester group to favor transition state **C**, which leads to the observed predominance for antiproducts (Figure 3a). Additionally, substituted allenes (R^2 ≠ H) prefer to avoid R^2/R^3 interaction in **B** and thus favor Z-alkene formation as observed. The observed lower Z-selectivity in product **17** can be explained by a less repulsive R^2/R^3 interaction. Despite using slight excesses of both allene and titanium tetrahalide, we have not observed byproducts formed by the addition of halogen to allenes (Figure 3b). This finding seems consistent with our concerted mechanistic model.

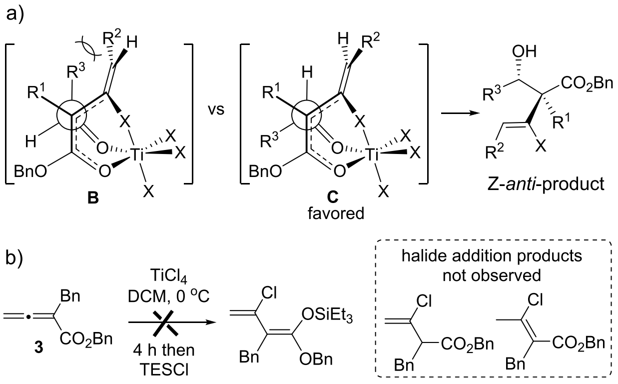
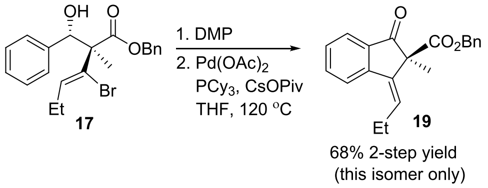


Figure 3. Current mechanistic hypothesis.

To explore some of the potential applications of the present halo aldol products, we sought to convert compound **17** to an indane in the presence of a palladium catalyst inspired by a C−H activation method developed by Liu.[23] Our initial efforts led to numerous side products; however, oxidation of alcohol followed by palladium-catalyzed coupling led to alkylidene indanone **19** (Scheme 2). Although related indanones have been efficiently synthesized by Kwon,[24] our approach leads to a novel compound not readily accessible using currently known methods.

Scheme 2. Elaboration of 17 into a Novel Alkylidene Indanone



In conclusion, β-hydroxy esters containing either tertiary or all-carbon quaternary α-centers were constructed using a variety of substituted allenoates as prenucleophiles. High diastereoselectivity was achieved for tertiary and especially quaternary center-containing products. Trisubstituted allenoates led to especially congested aldol products in good triple diastereoselectivity. Although mechanistic studies are ongoing, the relative stereochemistry of addition products appear to support a closed-transition-state mechanism. Our efforts on adapting this reaction to produce nonracemic products as well as an expansion of the indanone synthesis methodology will be published in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02930.

Characterization data for all new compounds and experimental procedures (PDF)

Accession Codes

CCDC 1903943 contains 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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Notes

The authors declare no competing financial interest.

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