Asymmetric Synthesis of γ -Hydroxy α , β -Unsaturated Aldehydes via Enantioselective Direct Addition of Propargyl Acetate to Aldehydes

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ABSTRACT



We report the first example of enantioselective and diastereoselective aldehyde additions of propargyl acetate to aldehydes using the methodology recently reported from our laboratories. Subsequent *O*-silyl protection, Pd-catalyzed isomerization, AcOH addition, and hydrolysis result in optically active γ -hydroxy $\alpha_{,\beta}$ -unsaturated aldehydes as powerful building blocks.

Chiral allylic alcohols are powerful building blocks for asymmetric synthesis as they possess useful stereodirecting influence in a number of chemical transformations such as hydroxyl-directed epoxidations, cyclopropanations, and hydrogenation. The presence of a carbonyl functionality in conjugation with a C=C bond widens the scope of application and synthetic importance of this class of compounds to include 1,4-additions and cyclizations.¹ In this respect, γ -hydroxy α , β -unsaturated carbonyl compounds provide

direct access to natural products, such as the oxylipins (e.g., constanolactones A and B)² or hybrid antibiotics (e.g., decarestrictine D).³ A variety of methodologies have been reported for the synthesis of γ -hydroxy α , β -unsaturated carbonyl derivatives, including asymmetric dihydroxylation and subsequent dehydration of β , γ -unsaturated carbonyl derivatives,⁴ photoinduced rearrangement of α , β -epoxy diazomethyl ketones,⁵ olefination of α -hydroxy aldehydes,⁶ and condensations of optically active sulfinyl acetates with aldehydes (the "SPAC" reaction).⁷ Herein we report an atomeconomical process that provides ready access to optically

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active γ -hydroxy α , β -unsaturated aldehydes. The process combines two modern synthetic methods: (1) the direct, enantioselective addition of propargyl acetate to aldehydes mediated by Zn(II), Et₃N, and (+)- or (-)-*N*-methylephedrine to afford optically active propargylic alcohols followed by (2) Pd-catalyzed rearrangement and addition of HOAc (Scheme 1).



Recently, we have been interested in the synthesis of optically active propargylic alcohols via the enantioselective direct addition of terminal alkynes to aldehydes.⁸ This method constitutes a powerful means to access chiral propargyl alcohols, which are potent intermediates for the synthesis of a variety of natural products and macromolecules.⁹ Using this process we have effected the direct addition of propargyl acetate to various aldehydes. As shown (Scheme 2 and Table 1), the corresponding chiral propargylic



alcohols were obtained in useful yields and excellent selectivities. As we have previously described, for the addition reactions involving stoichiometric use of Zn(II) and *N*-methylephedrine, the individual reactions can be fine-tuned for any specific substrate in an effort to optimize rate, yield, and selectivities.^{8c}

Because the addition reaction to α -alkoxy acetaldehyde (entry 4) represents the first time we have investigated chiral aldehyde substrates, we carried out some investigations to probe the extent of reagent versus substrate control. In this regard, the addition to (*S*)-2-(*tert*-butyldimethylsilyloxy)-

Table 1. Enantioselective Additions of 2-Propargyl Acetate **7** to Aldehydes $1-6^{a,b}$

entry	R	yield (8–13)	selectivity
1	<i>i</i> -Pr	95% (8)	96% ee
2	$c - C_6 H_{11}$	88% (9)	97% ee
3	t-Bu-CH ₂	68% (10)	97% ee
4	(S)-CH ₃ CH(OTBS)	70% (11)	97:4 dr
5	$\mathbf{P}\mathbf{h}^d$	57% (12)	97% ee
6	TBSOCH ₂ ^e	54% (13)	88% ee

^{*a*} The addition reaction was conducted using 1.1 equiv of $Zn(OTf)_2$, 1.2 equiv of (+)-*N*-methylephedrine, 1.2 equiv of Et₃N, and 1.2 equiv of propargyl acetate in toluene at room temperature. ^{*b*} Following addition of aldehyde, the reaction times were 4–5 h for entries 1–4 and 16 h for entry 5; for entry 6, the aldehyde was added over 24 h. ^{*c*} The % ee was determined by conversion of the adducts to the corresponding Mosher (*R*)-MTPA esters. In all cases, the ¹⁹F NMR of both enantiomers were determined. ^{*d*} Using 4.2 equiv of Zn (OTf)₂, 3.2 equiv of (+)-*N*-methylephedrine, 3.2 equiv of Et₃N, 3.2 equiv of Zn (OTf)₂, 2.2 equiv of (+)-*N*-methylephedrine, 2.2 equiv of Et₃N, 2.2 equiv of propargyl acetate in toluene at room temperature.

propanal **4** mediated by (+)-*N*-methylephedrine furnished adduct as a 26:1 syn/anti mixture of diastereomers in 70% yield, favoring the 1,2-syn stereochemical outcome. By contrast, the use of (-)-*N*-methylephedrine, under otherwise identical conditions, afforded the product possessing 1,2anti diastereomeric relationship in 69% yield (syn/anti 1:10) as shown in Scheme 3. The influence of the resident chiral



center on the stereochemistry of addition was examined in addition reactions employing the achiral amino alcohol 2-methyl-2-(N,N-dimethylamino)propanol, in which case the stereochemical outcome was found to favor the 1,2-syn diastereomer, with the same preference as (+)-N-methyl-ephedrine, albeit with considerably diminished diastereose-lectivity. The results of these experiments provide an initial indication that in diastereoselective addition reactions dominant stereochemical control is provided by the chiral amino

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 Table 2.
 Protection and Pd-Catalyzed Reactions^{a,b}

entry	R	yield (15–20)	yield (21–26)
1	<i>i</i> -Pr	90% (15)	85% (21)
2	$c - C_6 H_{11}$	90% (16)	75% (22)
3	t-BuCH ₂	95% (17)	83% (23)
4	(S)-CH ₃ CH(OTBS)	94% (18)	73% (24)
5	Ph	88% (19)	42% (25)
6	TBSOCH ₂	58% (20)	55% (26)

^{*a*} All reactions were performed using 2 mol % Pd₂(dba)₃•CHCl₃, 23 mol % Ph₃P, and 1.75 equiv of AcOH in refluxing toluene for 48 h. ^{*b*} All yields refer to isolated chromatographically purified compounds.

alcohol employed, with the resident stereogenic center of the aldehyde playing a subordinate role.¹⁰

Having ready access to the optically active propargylic diols, we subsequently investigated the use of these substrates in Pd-catalyzed rearrangements. The palladium-catalyzed reactions of propargylic compounds in organic synthesis constitute an important class of transformations in the organometallic repertoire for both synthetic and methodological interest.¹¹ To this end we envisioned the use of Trost's palladium-catalyzed rearrangement and addition reaction¹² with the aforementioned chiral propargyl addition products. Very recently, Trost has reported the first two examples of the Pd-catalyzed isomerization and HOAc addition applied to chiral substrates.^{12b} In our concurrent and independent study, reaction of 2 mol % of Pd₂(dba)₃·CHCl₃ with triphenylphosphine (23 mol %) in toluene together with acetic acid and the protected propargylic alcohols 15-20 at reflux resulted in the formation of gem-diacetates 21-26 as illustrated in Scheme 4 and Table 2.



In our investigation of this reaction chemistry the use of the TBS-protected secondary alcohol derivative resulted in the formation of the corresponding *gem*-diacetate derivative, albeit in only 55% yield for R = i-Pr. Through the use of

Table 3. Hydrolysis of the *gem*-Diacetates 21-26 to the Corresponding Aldehydes $27-32^{a,b}$

entry	R	yield (27–32)
1	<i>i</i> -Pr	94% (27)
2	$c - C_6 H_{11}$	97% (28)
3	t-BuCH ₂	87% ^c (29)
4	(S)-CH ₃ CH(OTBS)	99% (30)
5	Ph	88% (31)
6	TBSOCH ₂	77% (32)

^{*a*} All reactions were performed using 3.2 equiv of dry Et₃N in methanol overnight at room temperature (unless otherwise stated). ^{*b*} Yields refer to isolated, chromatographically purified compounds. ^{*c*} Reaction conducted at 45 °C.

the bulkier TBDPS protecting group, Pd-mediated oxidative addition across the C–H bond is directed away from the secondary propargyl alcohol toward the sterically less encumbered primary alcohol protected as an acetate. Consequently, it is evident that the size of the *O*-protecting group plays an important role in influencing the selective activation of the propargylic C–H. The effect of changing the silyl protecting group has been independently confirmed by Trost.^{12b}

As outlined in Table 2, *gem*-diacetates were obtained in good yields (21-24) except for the aromatic and aliphatic α -unbranched derivatives (25 and 26), which afforded the product in moderate yields.¹³

Finally, conversion of the diacetates 21-26 to the corresponding required optically active γ -hydroxy α , β -unsaturated aldehydes 27-32 and was accomplished by base-mediated hydrolysis of the *gem*-diacetates using Et₃N in methanol, as summarized in Scheme 5 and Table 3.



In conclusion, the method recently developed in our laboratories to effect the enantioselective addition of alkynes to aldehydes can be performed with propargyl acetate. As part of this work, we have investigated the first example of addition of an alkyne to a chiral aldehyde using our methodology; initial results indicate that the stereochemical outcome is reagent-controlled. When propargyl acetates are subjected to Pd-catalyzed rearrangement and HOAc addition, access to useful building blocks is provided in the form of γ -hydroxy $\alpha_{,\beta}$ -unsaturated aldehydes. This present investiga-

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tion demonstrates the general applicability of the Pdcatalyzed rearrangement and addition reaction to optically active substrates, providing a powerful example of the new types of chiral building blocks that can be accessed when modern synthetic methods are employed in sequence. **Acknowledgment.** Support has been provided by generous funds from the ETH.

Supporting Information Available: Full characterization and experimental procedures for the synthesis of the chiral propargylic alcohols, *tert*-butyldiphenylsilyl protected propargylic alcohols, the *gem*-diacetate derivatives, and the corresponding *O*-silyl protected γ -hydroxy α , β -unsaturated aldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹³⁾ To the best of our knowledge, at the time that this work was conducted there were no examples of the Pd-catalyzed isomerization and HOAc addition utilizing chiral substrates, so it was important to confirm that enantiopurity was maintained during this reaction. This was checked by desilylating **15** using either TBAF or TBAT to afford the corresponding allylic alcohol which was found to have an unchanged enantiopurity of 96% ee (determined by ¹⁹F NMR of the corresponding Mosher ester).