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Preparation of Chiral α-Substituted Alaninates through an Efficient Diastereoselective Synthesis of Trisubstituted Allylic Alcohols

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Chiral glyceraldehydes are not only extensively used as substrates in studying the stereochemistry of nucleophilic addition reactions, but are also useful three-carbon building blocks for the preparation of optically active organic molecules.[1] Isopropylidene glyceraldehydes are frequently used for such a purpose because of their ease of preparation from readily available chiral pool starting materials of both enantiomers, such as D-mannitol,[2] L-mannitol,[3] L-ascorbic acid, and D-isoascorbic acid.[4] However, owing to the undesirable racemization, polymerization, and a high tendency to form hydrates,[5] a number of analogues that bear various ketal protecting groups have been developed.[6] Ley et al. recently introduced stable butane-2,3-diacetal-protected glyceraldehydes **1**[7] to alleviate these long-standing problems and demonstrated their utility in the synthesis of complex natural products (Figure 1).[7d] The stereoelectronic effects direct

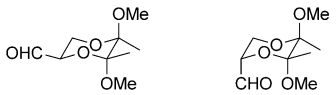
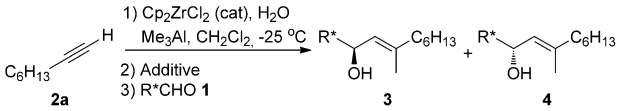


Figure 1. Chiral butane-2,3-diacetal glyceraldehydes **1**.

the two methoxy groups in the axial position, thereby giving rise to a more rigid six-membered cyclic structure. Thus, a high stereoselectivity is observed, partly because of chelation of the magnesium ion with the axial methoxy groups, in the nucleophilic addition of a variety of Grignard reagents to (2*S*,5*R*,6*R*)-5,6-dimethyl-[1,4]dioxane-2-carbaldehyde (**1b**), thus affording the corresponding secondary alcohols in high yields and excellent diastereoselectivities.[7a] However, the use of aldehydes **1** as substrates with other nucleophiles has, since the work of Ley et al., received less attention. In our recent studies on diastereoselective addition reactions of trisubstituted vinylalane reagents, that were obtained from a Zr-catalyzed carboalumination reaction of terminal alkynes and Me_3Al, with chiral 2,3-*O*-isopropylidene- and cyclohexylidene glyceraldehydes, the allylic alcohols were generally obtained in good yields but in moderate diastereoselectivities (up to 77% d.r.).[8] To employ the resulting chiral trisubstituted *E*-allylic alcohols as critical intermediates in the synthesis of some complex natural products, the stereoselectivity must be improved.[9] In this study, aldehydes **1** were examined in an attempt to improve the diastereoselectivity of the described reactions of interest.

In the initial trial, the diastereoselective addition reaction of glyceraldehyde **1a**, prepared from D-mannitol,[7a] was carried out with the vinylalane reagent that was synthesized according to Wipf's protocol.[10] The rapid Zr-catalyzed carboalumination of 1-octyne (**2a**) with Me_3Al in the presence of water furnished the active (*E*)-2-methyl-1-octenyl aluminum reagent, to which **1a** was added, and the corresponding trisubstituted *E*-allylic alcohols (**3aa** and **4aa**) were obtained in an overall yield of 39% with poor diastereoselectivity (Table 1, entry 1). The products, derived from aldehyde **1b**, were obtained in 43% yield with an improved diastereoselectivity (**3ba**/**4ba** = 80:20; Table 1, entry 4).[11] While the addition of a slight excess of Me_3Al enhanced the diastereoselectivity, as found by the research group of Spino,[12] the diastereomeric ratio of isomers was further improved (**3aa**/**4aa** = 86:14) by adding MeLi (1.5 equiv) after the preparation of the vinylalane reagent (Table 1, entry 2). Presumably, the corresponding Al–ate complex was formed upon the addition of MeLi, thereby enhancing the nucleophilicity of the corresponding vinylalanate.[13] The yield was subsequently

Table 1. Addition of vinylalane to chiral glyceraldehydes **1**.[a]



Entry	Aldehyde	Additive	Yield [%][b]	d.r. (**3**/**4**)[c]
1	**1a**	none	39	55 (**3aa**):45 (**4aa**)
2	**1a**	MeLi[d]	39	86 (**3aa**):14 (**4aa**)
3[e]	**1a**	MeLi[d]	89	89 (**3aa**):11 (**4aa**)
4	**1b**	none	43	80 (**3ba**):20 (**4ba**)
5[e]	**1b**	MeLi[d]	95	>99 (**3ba**):1 (**4ba**)

[a] Reaction conditions: Aldehyde (1.0 equiv), Me_3Al (3.3 equiv), Cp_2ZrCl_2 (0.22 equiv), H_2O (1.67 equiv) [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] MeLi (1.5 equiv) was added prior to the addition of aldehyde. [e] 3.0 equiv of (*E*)-2-methy-1-octenyl aluminum reagent was added.

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improved to 89% by using three equivalents of the vinylalanate reagent (Table 1, entry 3). Under the aforementioned optimal conditions, the addition of vinylalanate to aldehyde **1b** gave the corresponding allylic alcohol **3ba** in high yield (95%) with excellent stereoselectivity (>99:1) (Table 1, entry 5). The stereochemistry of the secondary alcohol **3ba** had the *R* configuration, as determined by Mosher's method (Figure 2).[14,15]

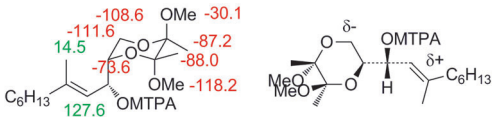
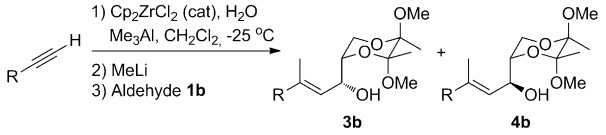
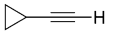
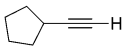
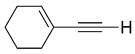


Figure 2. Determination of the absolute configuration of allylic alcohol **3ba** by employing Mosher's method.

By considering the above observations, the addition of various vinylalanates to aldehyde **1b** was examined under the reaction conditions that are specified in entry 5 of Table 1. As pointed out in Table 2, by adding vinylalanates

Table 2. Diastereoselective addition of various vinylalanes to aldehyde **1b**.[a]



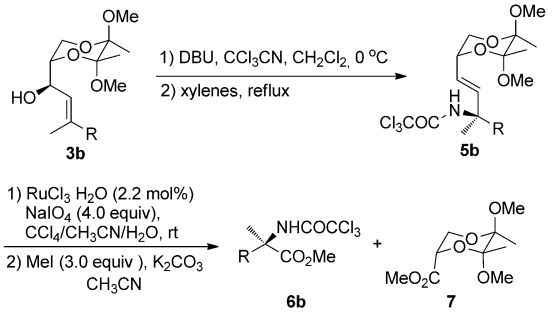
Entry	Alkyne		Yield [%][b]	d.r. (**3b**/**4b**)[c]
1	C_6H_{13}—≡—H	(**2a**)	95	>99 (**3ba**):1 (**4ba**)
2	C_5H_{11}—≡—H	(**2b**)	77	>99 (**3bb**):1 (**4bb**)
3	C_3H_7—≡—H	(**2c**)	95	>99 (**3bc**):1 (**4bc**)
4	$(CH_3)_2CH(CH_2)_2$—≡—H	(**2d**)	70	>99 (**3bd**):1 (**4bd**)
5	*t*Bu—≡—H	(**2e**)	72	>99 (**3be**):1 (**4be**)
6	Ph—≡—H	(**2f**)	96	>99 (**3bf**):1 (**4bf**)
7		(**2g**)	80	>99 (**3bg**):1 (**4bg**)
8		(**2h**)	93	>99 (**3bh**):1 (**4bh**)
9		(**2i**)	42	80 (**3bi**):20 (**4bi**)

[a] Reaction conditions: Aldehyde **1b** (1.0 equiv), Me_3Al (3.3 equiv), Cp_2ZrCl_2 (0.22 equiv), alkyne (3.0 equiv), H_2O (1.67 equiv), MeLi (1.5 equiv). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy.

that were derived from alkynes bearing alkyl substituents furnished the 1,2-adducts in high yields (77–95%) and excellent diastereoselectivity (>99:1), regardless of the carbon chain length of the alkyl substituents (Table 2, entries 1–3). Similar results were also obtained when branched substituted alkynes, such as 5-methyl-1-hexyne (**2d**) and 3,3-dimethyl-1-butyne (**2e**) (Table 2, entries 4 and 5) were used. A nucleophilic vinylaluminum reagent that was prepared from phenylacetylene (**2f**) was an effective nucleophile, and provided the corresponding allylic alcohol **3bf** in both excellent yield (96%) and diastereoselectivity (**3bf**/**4bf** = >99:1; Table 2, entry 6). Additionally, trisubstituted *E*-allylic alcohols (**3bg** and **3bh**) obtained by the addition of vinyl nucleophiles that were substituted with three and five membered rings, were isolated in high yields and diastereoselectivities (Table 2, entries 7 and 8). Notably, the cyclopropyl ring remained unaltered after a Zr-catalyzed carboalumination reaction, yielding the desired product **3bg** (Table 2, entry 7). In contrast, the Zr-catalyzed carboalumination of an alkyne that had a cyclohexene substituent proceeded sluggishly, and formed the corresponding adduct, but in only moderate yield (42%) and diastereoselectivity (**3bi**/**4bi** = 80:20; Table 2, entry 9). Presumably, in the presence of an olefin, the Zr-catalyzed carboalumination reaction with the alkyne functional group proceeds but it competes with the alkene during the catalytic cycle, thereby complicating the overall process.[16]

This developed methodology was further exploited in the synthesis of methyl α-substituted alaninates (Table 3).[17] The

Table 3. Syntheses of α-substituted alaninates.

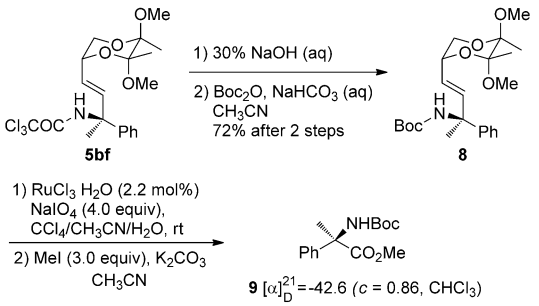


Entry	R	Allylic Amine **5b** Yield [%][a]	d.r. [b]	Alaninate **6b** Yield [%][a]	*ee* [%][c]
1	Hexyl	52 (**5ba**)	>99:1	67 (**6ba**)	>99
2	*i*Pentyl	46 (**5bd**)	>99:1	63 (**6bd**)	>99
3	*t*Bu	65 (**5be**)	>99:1	74 (**6be**)	>99.5
4	Ph	72 (**5bf**)	>99:1	89 (**6bf**)	>99.5
5	cyclopropyl	N.O.[d]	N.D.[e]	N.D.[e]	N.D.[e]
6[d,e]	cyclopentyl	N.O.[d]	N.D.[e]	N.D.[e]	N.D.[e]

[a] Yield of isolated product. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] Not observed. [e] Not determined.

preparation of these non-proteogenic amino esters has attracted considerable interest because of their biological activity in inhibiting certain types of enzymes[18] and their ability to modify the conformations of biologically active peptides.[19] As illustrated in Table 3, the trisubstituted chiral allylic alcohol **3ba** was converted into the allylic amine **5ba** by following Overman's method.[20] Thus, compound **3ba** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and CCl_3CN, and then a thermal Overman rearrangement took place in two steps to provide the allylic amine **5ba** as a single diastereoisomer in 52% yield (Table 3, entry 1). The Ru^{III}-catalyzed oxidative cleavage of compound **5ba** furnished the corresponding butane-2,3-diacetalglyceric acid

and highly enantioenriched α-methyl α-hexyl amino acid; both of these compounds were treated with iodomethane under basic conditions to yield the corresponding methyl amino ester **6ba** in 67% yield and >99% *ee*[21] as well as the methyl ester **7** (>90% yield). Following the establishment of a reliable sequence for transforming allylic alcohol **3ba** into a chiral quaternary alaninate **6ba**, the preparation of α-substituted alaninates bearing diverse substituents from allylic alcohols that were obtained from a diastereoselective addition reaction has been demonstrated (Table 3, entries 2–4). Despite the fact that [3,3]-sigmatropic rearrangements of chloroimidates that are derived from allylic alcohols **3bg** and **3bh** do not give the desired allylic amine derivatives,[20a,d,22] the four-step transformation described here further increased the utility of this sequence to afford methyl amino esters (**6bd**–**6bf**) with high yields (63–89%) and excellent enantioselectivity (>99% *ee*).[23] Furthermore, the stability of the allylic amine **5bf** with a quaternary center was demonstrated in a two-step transformation to the corresponding *tert*-butyloxycarbonyl (Boc)-protected allyl amine **8**. The two steps were 1) the base-mediated removal of the trichloroacetyl protecting group[24] and then 2) Boc protection.[25] Subsequent catalytic oxidative cleavage and esterification efficiently provided the *N*-Boc-α-methyl-α-phenylglycine methyl ester (**9**) with a high optical purity (99% *ee*; Scheme 1).[26,27]



Scheme 1. Synthesis of chiral *N*-Boc-α-phenyl alaninate **9**.

In conclusion, an efficient method for the synthesis of trisubstituted *R,E*-allylic alcohols with high selectivity from the reaction of aldehyde **1b** with trisubstituted vinylalanates has been reported. The trisubstituted vinylalanates were prepared by treating MeLi with the trisubstituted vinylalanes that were synthesized by a Zr-catalyzed carboalumination of various terminal alkynes with Me_3Al. The chiral trisubstituted allylic alcohols thus obtained were transformed into allylic amines that contained a quaternary stereogenic carbon center by the thermal Overman rearrangement of the allylic trichloroimidates. This method can be further extended to the asymmetric synthesis of both enantiomeric isomers of α-substituted alaninate methyl esters with >99% *ee*, as both the enantiomers of aldehyde **1b** are readily available from the chiral pool. This work provides an efficient route for synthesizing highly enantioenriched quaternary α-amino acid derivatives and is potentially useful in the synthesis of optically active compounds that have quaternary chiral centers. Studies toward the preparation of substituted cyclic alaninates are currently being intensively investigated.

Experimental Section

At room temperature, Cp_2ZrCl_2 (17 mg, 0.058 mmol, 0.22 equiv) and dry CH_2Cl_2 (5 mL) were added to a dry 10 mL round bottom flask under an argon atmosphere, and it was cooled to −25 °C. Me_3Al (0.81 mL, 1.0 M in heptanes, 0.81 mmol, 3.33 equiv) was slowly added to this mixture, and after being stirred for an additional 30 min, water (7.3 μL, 0.40 mmol, 1.67 equiv) was slowly added at −25 °C. After an additional 30 min, a solution of 1-octyne (**2a**) (0.11 mL, 0.73 mmol, 3 equiv) in dry CH_2Cl_2 (3 mL) was added dropwise over 10 min and after 30 min, MeLi (0.17 mL, 2.2 M in toluene, 0.37 mmol, 1.5 equiv) was added. A solution of *S*-aldehyde **1b** (50 mg, 0.244 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was introduced at −25 °C over 30 min. After the whole mixture was stirred at the same temperature for 3.5 h, the temperature was slowly raised to room temperature, and was then cooled to 0 °C 1 h later. The reaction was quenched by adding a sat. aq. K_2CO_3 solution, and 10 min later, a 2 N HCl solution was added to neutralize the solution to pH 7. The aqueous layer was separated and extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was dried over anhydrous $NaSO_4$ and concentrated under reduced pressure to give the crude product. The crude compound was purified by flash column chromatography (EA/hexanes 1:9) to afford the pure compound **3ba** in 95% yield.

Acknowledgements

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Keywords: allylic compounds · amines · butane-1,2-diacetal-protected L-glyceraldehyde · diastereoselectivity · α-substituted alaninates

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[22] Both thermal, Hg^{II}- and Pd^{II}-catalyzed rearrangement of trichloroimidate derived from allylic alcohol **3bg** and **3bh** led to the decomposition of starting material.
[23] The coupling constants of the two olefinic protons at 5.8 and 5.9 ppm for compounds **5ba**, **5be**, and **5bd**, and at 6.1 and 6.2 ppm for **5bf** were 16.0 and 15.8 Hz, respectively, clearly indicating the presence of two *trans*-olefinic protons; see the Supporting Information.
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