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Reaction of Optically Active α-Aminoallenylstannanes with Aldehydes Formed in Situ from the Lewis-Acid-Catalyzed Rearrangement of Epoxides

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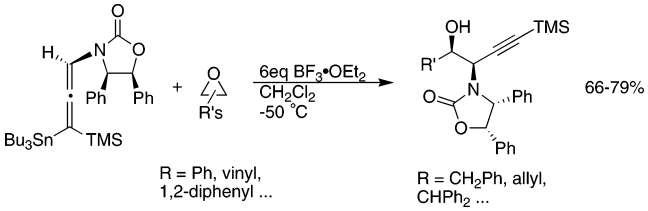


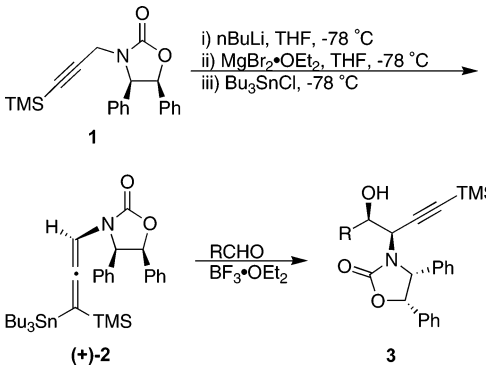
Reaction of optically active α-oxazolidinonylallenylstannanes with oxiranes in the presence of BF_3·OEt_2 produced β-hydroxypropargylamines with high syn diastereoselectivity and high enantioselectivity through an initial Lewis-acid-catalyzed rearrangement of the oxirane to the corresponding aldehyde via an alkyl, aryl, or hydride shift. This permits the use of readily available oxiranes as alternatives to aldehydes that are difficult to prepare and/or unstable.

On the basis of the pioneering and extensive work of Marshall on the reactivity of allyl-, propargyl-, and allenylstannanes,[1] an efficient synthesis of optically active α-oxazolidinonylallenylstannanes and their highly diastereo- and enantioselective reaction with aldehydes was recently reported from these laboratories.[2] The synthesis involved regio- and stereoselective stannylation of TMS-protected propargyloxazolidinone **1**, followed by Lewis-acid-catalyzed reaction with aldehydes (Scheme 1). The reaction proceeded with high syn diastereoselectivity and high enantioselectivity and was virtually insensitive to α-chirality on the aldehyde substrate. The resulting α-hydroxypropargyloxazolidinones **3** were converted to γ-hydroxy-β-amino acids, one of which was used in the total synthesis of 1-deoxy-D-galactohomonojirimycin.[2b] Attempts to extend this chemistry to oxirane substrates are presented below.

Studies commenced with the BF_3·OEt_2-catalyzed reaction of allenylstannane (+)-**2** with styrene oxide (Scheme 2). Remarkably, neither of the expected β-hydroxypropargyloxazolidinones **4** were obtained. Instead, the α-hydroxy product **5a**, which corresponds to the reaction with phenylacetaldehyde, was obtained in good yield and excellent diastereoselectivity (the structure of **5a** was confirmed by using phenylacetaldehyde as a substrate, which gave the same product). Compound **5a** most likely arises by the BF_3·OEt_2-catalyzed rearrangement of the styrene oxide to phenylacetaldehyde, followed by reaction with (+)-**2**. Lewis-acid-catalyzed rearrangements of epoxides to aldehydes via hydride or alkyl shifts to the developing carbocationic center resulting from epoxide ring opening are well-known,[3] as are Lewis-acid-catalyzed reactions with epoxides without rearrangement.[4] Under the conditions in Scheme 2, epoxide rearrangement must be faster than the reaction of (+)-**2** with the epoxide, while reaction of (+)-**2** with the aldehyde product is fast.

A variety of Lewis acids and conditions were screened to see if reaction of (+)-**2** with epoxides without rearrangement could be achieved. These included $SnCl_4$, $TiCl_4$, $ZrCl_4$, TMSOTf, and $B(C_6F_5)_3$, all of which were unsuccessful, resulting in either destannylation of (+)-**2**

SCHEME 1



SCHEME 2

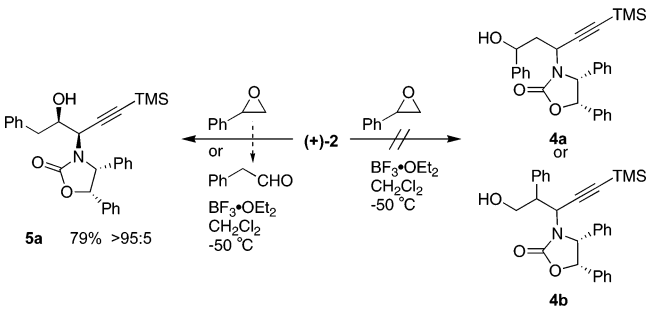


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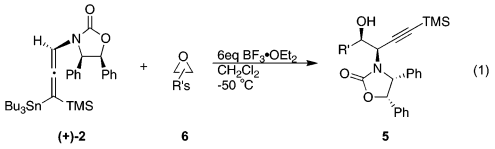
TABLE 1. Reactions of (+)-2 with Oxiranes (Eq 1)



Entry	Oxirane		Product,		Yield, %[a]	dr (*syn*/*anti*)[b]
1		**6a**	R'= $PhCH_2$	**5a**	79	>95:5
2		**6b**	R'= 	**5b**	66	>95:5
3		**6c**	R'= Ph_2CH	**5c**	74	94:6
4		**6d**	R'= 	**5d**	70	95:5
5		**6e**	R'= 	**5e**	73[c]	>95:5
6		**6f**	R'= 	**5f**	79	84:12:4[d]
7		**6f'**	R'= 	**5f'**	17[e]	90:10
8		**6g**	R'= CH_3CH_2	**5g**	traces	-
9		**6h**		-	NR	-
10		**6i**		-	NR	-
11		**6j**		-	NR	-

[a] Reported yields are for isolated, purified, single diastereoisomers. [b] Estimated from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Run at −78 °C for 12 h [d] Diastereomeric ratio for the full-syn:anti-CH_3:anti-OH compounds; stereochemistry of the main compound determined by single-crystal X-ray diffraction. [e] Substantial amounts of 1-phenylpropane-2-one was produced by migration, run using (±)-**2**.

to regenerate (−)-**1** or decomposition products. Tin(II) chloride promoted the reaction, again with ring-opening rearrangement of the epoxide, to give a 49% yield of α-hydroxypropargylamine **5a**, but as a 5:9 mixture of syn to anti diastereoisomers. Although *direct* reaction of (+)-**2** with epoxides was not achieved, the use of epoxides as aldehyde surrogates in cases for which the aldehyde is more difficult to synthesize than the corresponding epoxide, or is less stable, could still be synthetically useful. Thus, the scope of this epoxide rearrangement/aldehyde alkylation was explored (eq 1, Table 1).

The reaction proved to be efficient for oxiranes having a carbocation-stabilizing group at one terminus and a migrating hydride, phenyl, or alkyl chain. Thus, **5a** and **5f** (benzyl cation, migrating hydride), **5c** (benzyl cation, migrating phenyl), **5e** (benzyl cation, migrating alkyl chain), **5b** (allyl cation, migrating hydride), and **5d** (tertiary alkyl cation, migrating hydride) were all formed in good yield and with excellent diastereoselectivity. The formation of **5e**, which involved a six- to five-membered ring contraction, was efficient, while the corresponding rearrangement of cyclohexene oxide (**6h**, migration to a secondary carbocation) failed to occur, as did the reaction of propylene oxide. The five- to four-membered ring contraction failed even with **6j**, having a benzyl cation terminus, presumably because of ring strain.

The reaction of α-methylstyrene oxide (**6f**) provided additional insight into the process. Previous studies[2] had shown that the absolute configuration of the newly formed chiral center was insensitive to α-chirality in the aldehyde substrate, with high syn stereoselectivity being observed with both enantiomers of α-chiral aldehydes. Reaction of excess (±)-**6f** with (+)-**2** gave an 87:13 mixture of two *syn*-amino alcohol diastereoisomers **5f**, which differed in configuration at the γ-methyl group. The major diastereoisomer was the fully syn compound. This indicates that, although the absolute configuration of α-chiral aldehyde has little effect on the syn/anti ratio of amino alcohol formed, it does strongly influence the *rate* of aldehyde alkylation, with the matched combination[5] undergoing reaction roughly seven times faster than the mismatched combination. Reaction of (*S*)-(+)-**2** with *S*-α-methylstyrene oxide produced **5f** with the same diastereoisomeric ratio as that obtained with racemic epoxide, indicating that the epoxide rearrangement was not stereospecific. When both reactants (**2** and **6f**) were racemic, an 89:11 mixture of the same two (now racemic) syn diastereoisomers was obtained in 69% overall yield. In addition, the reaction with β-methylstyrene oxide **6f′** proceeded in low yield, accompanied by substantial amounts of 1-phenylpropane-2-one. This indicates that hydride migration was favored over methyl migration and, as previously observed,[2] ketones are not reactive toward allenylstannane **2**.

In summary, optically active α-oxazolidinonylallenylstannanes underwent Lewis-acid-catalyzed reactions with a range of oxiranes via rearrangement to the corresponding aldehyde followed by alkylation. With suitable epoxides, the process proceeded in good yield and with high diastereoselectivity. It should prove to be useful in synthesis in cases for which the oxirane is more readily accessible than the corresponding aldehyde.

Experimental Section

General Procedure for the Condensation of Allenylstannane (+)-2 with Oxiranes. Synthesis of (4*R*,5*S*)-*N*-[(3*R*,4*R*)-4-Hydroxy-5-phenyl-1-(trimethylsilyl)-1-pentyn-3-yl]-4,5-diphenyl-2-oxazolidinone 5a. To a stirred solution of allenylstannane (+)-**2** (100 mg, 0.16 mmol) and styrene oxide (55 μL, 0.48 mmol) in methylene chloride (1 mL) at −50 °C was added boron trifluoride diethyl etherate (121 μL, 0.96 mmol). The reaction was stirred at −50 °C for 1 h until no allenylstannane remained by TLC, quenched at −50 °C with saturated sodium bicarbonate (5 mL), and stirred for an additional time (0.5−1 h) while warming to room temperature. The reaction mixture was extracted with methylene chloride (10 mL), and the organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude reaction product. The diastereoselectivity of the reaction was determined to be >95:5. Purification through silica gel, eluting with 6:1 hexanes/ethyl acetate, gave the homopropargylic alcohol **5a** (59 mg, 79%) as a white solid. The diastereoselectivity of the reaction was determined to be >95:5. Mp: 173−174 °C. $[\alpha]^{22}_D$ −27.2 (*c* 1.2, CH_2Cl_2). IR (thin film) *ν*: 3417 (OH), 2200 (C≡C), 1733 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.37−7.31 (m, 5H), 7.07 (m, 6H), 6.92 (m, 4H), 5.77 (d, *J* = 7.5 Hz,

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1H), 5.23 (d, J = 7.5 Hz, 1H), 4.64 (d, J = 7.5 Hz, 1H), 4.28 (m, 1H), 3.16 (dd, J_1 = 14.1 Hz, J_2 = 3.3 Hz, 1H), 2.83 (dd, J_1 = 14.1 Hz, J_2 = 8.4 Hz, 1H), 2.41 (bs, 1H), −0.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 137.5, 134.7, 134.1, 129.5, 128.6, 128.0, 127.9, 127.9, 127.8, 127.7, 126.8, 126.2, 99.1, 93.4, 80.9, 73.6, 64.0, 51.9, 40.1, −0.5. MS (FAB$^+$) for $C_{29}H_{32}NO_3Si$ *m/z*: 470 (M + H$^+$, 100). Anal. Calcd for $C_{29}H_{31}NO_3Si$: C, 74.16; H, 6.65; N, 2.98. Found: C, 74.38; H, 6.66; N, 2.97.

(4*R*,5*S*)-*N*-[(3*R*,4*R*)-4-Hydroxy-1-(trimethylsilyl)-6-hepten-1-yn-3-yl]-4,5-diphenyl-2-oxazolidinone 5b. This compound was made according to the general procedure (T = −55 °C, t = 45′), using butadiene monoxide, which gave homopropargylic alcohol **5b** (44 mg, 66%) as a white solid. The diastereoselectivity of the reaction was determined to be >95:5. Mp: 197−199 °C. $[\alpha]^{22}_D$ −26.0 (*c* 1.5, CH_2Cl_2). IR (thin film) ν: 3485 (OH), 2200 (C≡C), 1730 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (m, 6H), 6.93 (m, 4H), 5.90 (m, 1H), 5.88 (d, J = 8.1 Hz, 1H), 5.26 (d, J = 8.1 Hz, 1H), 5.25 (m, 2H), 4.59 (d, J = 7.2 Hz, 1H), 4.08 (m, 1H), 2.60 (m, 1H), 2.56 (bs, 1H), 2.36 (m, 1H), −0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 134.7, 134.1, 133.4, 128.0, 128.0, 127.9, 127.8, 127.8, 126.2, 118.9, 99.0, 93.1, 80.9, 72.0, 64.0, 51.7, 38.1, −0.5. HRMS (FAB$^+$) (M + H$^+$) *m/z*: calcd for $C_{25}H_{30}NO_3Si$, 420.2003; found, 420.1995.

(4*R*,5*S*)-*N*-[(3*R*,4*R*)-5,5-diphenyl-4-hydroxy-1-(trimethylsilyl)-1-pentyn-3-yl]-4,5-diphenyl-2-oxazolidinone 5c. This compound was made according to the general procedure, using (±)-*cis*-stilbene oxide, which gave homopropargylic alcohol **5c** (65 mg, 74%) as a white solid. The diastereoselectivity of the reaction was determined to be 94:6. Mp: 84−87 °C. $[\alpha]^{22}_D$ + 5.1 (*c* 0.8, $CHCl_3$). IR (thin film) ν: 3435 (OH), 2190 (C≡C), 1731 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48−7.28 (m, 10H), 7.10−7.00 (m, 6H), 6.88 (m, 2H), 6.80 (m, 2H), 5.45 (d, J = 8.1 Hz, 1H), 5.00 (d, J = 8.1 Hz, 1H), 4.80 (m, 1H), 4.66 (d, J = 7.5 Hz, 1H), 4.50 (d, J = 5.4 Hz, 1H), 2.35 (brs, 1H), −0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 142.3, 139.4, 134.6, 134.0, 129.4, 129.4, 128.8, 128.7, 128.5, 127.9, 127.8, 127.7, 127.7, 127.2, 126.8, 126.1, 99.0, 93.9, 80.7, 74.4, 64.1, 53.3, 51.1, −0.5. MS (ES$^+$) for $C_{35}H_{35}NNaO_3Si$ *m/z*: 568 (M + Na$^+$, 100). Anal. Calcd for $C_{35}H_{35}NO_3Si$: C, 77.03; H, 6.46; N, 2.57. Found: C, 77.30; H, 7.05; N, 2.32.

(4*R*,5*S*)-*N*-[(3*R*,4*R*)-4-Cyclohexyl-4-hydroxy-1-(trimethylsilyl)-1-butyn-3-yl]-4,5-diphenyl-2-oxazolidinone 5d. This compound was made according to the general procedure, using methylenecyclohexane oxide,[6] which gave homopropargylic alcohol **5d** (52 mg, 70%) as a white solid. The diastereoselectivity of the reaction was determined to be >95:5. Mp: 227−229 °C. $[\alpha]^{22}_D$ + 12.6 (*c* 0.4, CH_2Cl_2). IR (thin film) ν: 3472 (OH), 2178 (C≡C), 1734 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (m, 6H), 6.95 (m, 4H), 5.86 (d, J = 7.8 Hz, 1H), 5.30 (d, J = 7.8 Hz, 1H), 4.74 (d, J = 6.6 Hz, 1H), 3.75 (m, 1H), 2.38 (bs, 1H), 1.95−1.60 (m, 5H), 1.56 (m, 1H), 1.26 (m, 5H), −0.10 (s, 9H). ^{13}C NMR (100 MHz, CDCl3) δ: 158.5, 134.7, 134.1, 128.1, 128.0, 127.9, 127.8, 127.8, 126.2, 99.6, 92.7, 80.9, 64.1, 49.6, 39.8, 29.8, 26.9, 26.3, 26.2, 26.0, −0.5. HRMS (FAB$^+$) (M + H) *m/z*: calcd for $C_{28}H_{36}NO_3Si$, 462.2464; found, 462.2464.

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(4*R*,5*S*)-*N*-[(3*R*,4*R*)-4-Hydroxy-4-(1-phenylcyclopentyl)-1-(trimethylsilyl)-1-butyn-3-yl]-4,5-diphenyl-2-oxazolidinone 5e. This compound was made according to the general procedure (stirring overnight at −78 °C), using 1-phenylcyclohexene oxide,[7] which gave homopropargylic alcohol **5e** (61 mg, 73%) as a white solid. The diastereoselectivity of the reaction was determined to be > 95:5. Mp: 182−184 °C. $[\alpha]^{22}_D$ −68.5 (*c* 1.8, $CHCl_3$). IR (thin film) ν: 3410 (OH), 2181 (C≡C), 1729 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.25 (m, 1H), 6.96 (m, 6H), 6.74 (m, 4H), 4.87 (d, J = 8.1 Hz, 1H), 4.77 (d, J = 4.8 Hz, 1H), 4.46 (d, J = 8.1 Hz, 1H), 4.04 (dd, J_1 = 5.4 Hz, J_2 = 4.8 Hz, 1H), 2.48 (d, J = 5.4 Hz, 1H), 2.42 (m, 1H), 2.16 (m, 2H), 1.92 (m, 1H), 1.70 (m, 3H), 1.44 (m, 1H), −0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 142.6, 134.9, 134.2, 128.5, 128.0, 128.0, 127.7, 127.5, 127.5, 126.5, 126.0, 100.6, 92.6, 81.2, 80.0, 64.0, 54.6, 48.8, 40.0, 34.6, 23.0, 22.6, −0.6. MS (ES$^+$) for $C_{33}H_{37}NNaO_3Si$ *m/z*: 546 (M + Na$^+$, 100), 524 (M + H$^+$, 29), 372 (41). Anal. Calcd for $C_{33}H_{37}NO_3Si$: C, 75.68; H, 7.12; N, 2.67. Found: C, 75.84; H, 7.30; N, 2.73.

(4*R*,5*S*)-*N*-[(3*R*,4*R*,5*S*)-4-Hydroxy-5-phenyl-1-(trimethylsilyl)-1-hexyn-3-yl]-4,5-diphenyl-2-oxazolidinone 5f. This compound was made according to the general procedure [(+)-**2**, 77 mg, 0.12 mmol], using (±)-α-methylstyrene oxide, which gave homopropargylic alcohol **5f** (46 mg, 79%) as a mixture of epimers in C5 of the hydrocarbon chain, with a ratio of 87:13. The major epimer was isolated as a colorless crystal by recrystallization. The diastereoselectivity of the reaction was determined to be 95:5. The absolute configuration of **5f** was resolved by single-crystal X-ray diffraction. Mp: 131−133 °C. IR (thin film) ν: 3421 (OH), 2182 (C≡C), 1732 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (m, 5H), 7.07 (m, 6H), 6.89 (m, 2H), 6.81 (m, 2H), 5.55 (d, J = 7.8 Hz, 1H), 4.99 (d, J = 7.8 Hz, 1H), 4.62 (d, J = 7.2 Hz, 1H), 4.22 (m, 1H), 3.24 (m, 1H), 2.47 (d, J = 6.3 Hz, 1H), 1.37 (d, J = 7.2 Hz, 3H), −0.06 (s, 9H). ^{13}C NMR (75.2 MHz, $CDCl_3$) δ: 158.3, 144.1, 134.5, 134.1, 128.7, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 126.8, 126.1, 99.0, 93.2, 80.8, 76.2, 64.1, 50.8, 41.7, 15.3, −0.5. Anal. Calcd for $C_{30}H_{33}NO_3Si$: C, 74.50; H, 6.88; N, 2.90. Found: C, 74.57; H, 7.01; N, 2.84.

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Supporting Information Available: Experimental details, ^{1}H and ^{13}C NMR spectra of **5b** and **5d**, and X-ray structural data for **5f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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