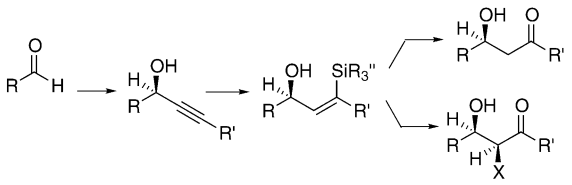
Regioselective Hydrosilylation

Regioselective Hydrosilylation of Propargylic Alcohols: An Aldol Surrogate**

Barry M. Trost, Zachary T. Ball, and Thomas Jöge*

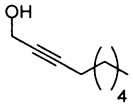
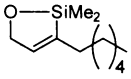
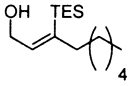
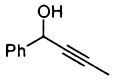
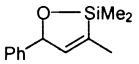
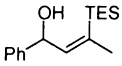
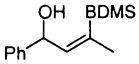
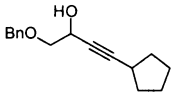
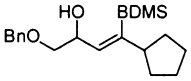
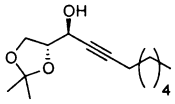
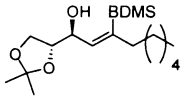
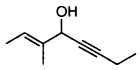
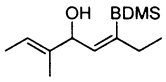
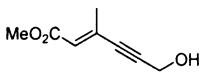
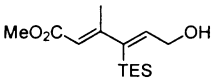
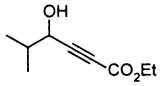
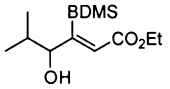


(1)

The aldol reaction has emerged as one of the most powerful ways to assemble complex targets with high stereochemical control in both a relative and an absolute sense. Despite the tremendous successes, deficiencies exist. As aldol adducts are prone to further reactions such as elimination, further substitution at the α-carbon becomes difficult.[1] Asymmetric additions of methyl alkyl ketones have been very limited.[2] Propargylic alcohols can become surrogates for aldols provided that a chemo- and regioselective introduction of a carbonyl group at the alkyne carbon β to the alcohol can be performed. The asymmetric access[3,4] to propargylic alcohols makes this approach an attractive alternative to the asymmetric aldol reaction. Although the direct hydration of a propargylic alcohol is a potentially attractive solution, the difficulty of obtaining regioselectivity as well as of avoiding elimination of the hydroxy ketone product under generally acidic hydration conditions led us to another approach.[5] As outlined in Equation 1, we chose to pursue selective incorporation of a vinyl C–Si bond, which can serve as a versatile ketone precursor.

During the course of our studies of the ruthenium-catalyzed hydrosilylation of alkynes,[6] our attention was drawn to the regioselective hydrosilylation of internal alkynes.[7,8] For some systems the regioselectivity could be simply resolved by tethering the silyl group, wherein a most interesting *endo*-selective intramolecular hydrosilylation occurred.[8a] Unfortunately, such a strategy failed with propargyl alcohols. We, therefore, hoped to harness the electronic bias—or perhaps catalyst ligation—of unprotected propargylic alcohols to effect regiochemical and geometrical selectivity in ruthenium-catalyzed *trans* hydrosilylation using $[Cp^*Ru(NCCH_3)_3]^+PF_6^-$ (**1**, $Cp^* = C_5Me_5$).

Table 1: Hydrosilylation of propargylic alcohols catalyzed by **1**.[a]

Entry	Alkyne	Silane[b]	**1** [mol%]	Major product	Yield,[c] sel.[d]
1[e]		A	2.5		30%,[f] n.d.
2[e]		B	1.0		99%, 13:1
3[e]		A	3.0		73%,[f] 5:1
4[e]		B	2.0		91%, 20:1
5		C	2.0		91%,[f] 14:1
6[e]		C	3.0		96%, 9:1
7		C	4.0		8%, 6:1
8		C	2.0		65%,[f] 5:1
9		B	5.0		63%[f] (84),[g] >20:1
10		C	2.0		83%,[f] 8:1

[a] All reactions were performed with 1.2 equiv silane in acetone from 0°C to room temperature and were complete within 30 min unless otherwise indicated. [b] A = $Me_2(EtO)SiH$, B = Et_3SiH (TES-H), C = $BzMe_2Si$-H (BDMS-H). [c] Yield of both isomers isolated except where indicated. [d] Regiochemistry of silane addition from NMR spectrum of the crude product. [e] Performed with 2.5 equiv silane in CH_2Cl_2. [f] Yield of pure major isomer isolated. [g] Numbers in parenthesis refer to yields based on recovered starting material.

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Initial experiments with $(EtO)_3SiH$ and 2-nonyn-1-ol catalyzed by complex **1** produced only extensive decomposition. On the other hand, the reaction of monoalkoxysilane $Me_2(EtO)SiH$ (Table 1, entry 1) gave the β-silyl compound, but mediocre selectivity and poor product stability led to yields of only about 30%. A bulkier secondary alcohol greatly improved product stability, and the desired vinylsilane was isolated in respectable yield (entry 3). A switch to triethylsilane (TES-H) improved the situation dramatically, and the

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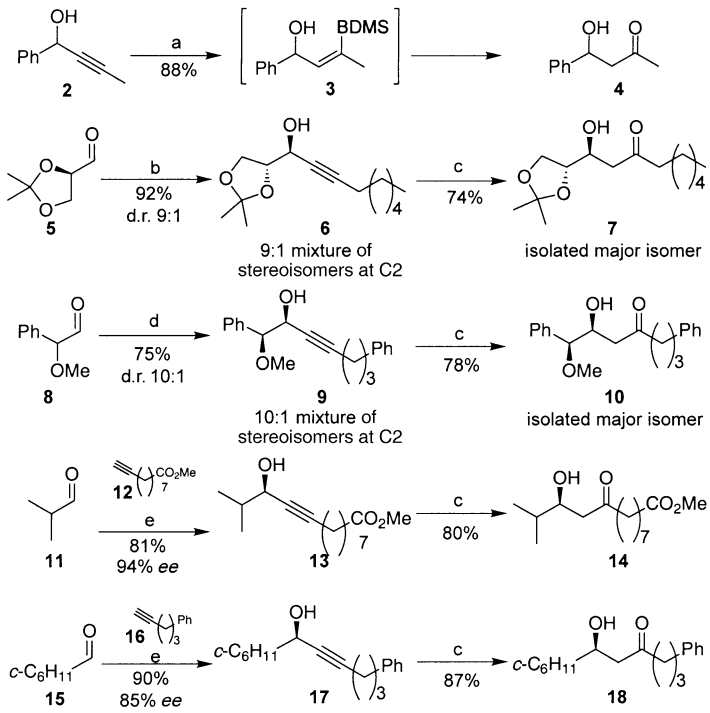
desired vinylsilanes could be produced in excellent yield with synthetically useful regioselectivity without any product stability issues (entries 2 and 4). In this and in all cases, only the *Z* products of *trans* addition are observed for the two regioisomers.

Although for some subsequent applications triethylvinylsilanes are suitable, we sought a silane that would maintain this clean reactivity and still permit a wide variety of subsequent operations. In our hands, the optimal choice was benzyldimethylsilane (BDMS-H), which we found to react in a manner very similar to triethylsilane, requiring only slightly higher catalyst loadings (generally 2–4%). The propargylic alcohol substrate itself also displays some unique reactivity. Conjugated alkene units and nearby double bonds lead to generally inferior results in the hydrosilylation reaction with **1**, but the substrates in entries 8 and 9 show meaningful reactivity. Entry 10 demonstrates that propargylic alcohols do not overcome the preference for silylation β to conjugated carbonyl groups, and the vinylsilane of opposite regiochemistry is obtained.

Having achieved selective formation of the necessary vinylsilanes, we sought to, first, unmask the ketone through oxidation and, second, utilize the vinylsilane as a handle for functionalization at the α-carbon atom. A key question becomes the fate of the presumed initial oxidation product. Since oxidation of the BDMS group of β-silyl allylic alcohols produces the enol of a β-hydroxy ketone, dehydration may accompany the unmasking.[9] Gratifyingly, elimination did not compete when methanolic basic hydrogen peroxide was used after initial debenzylation with tetrabutylammonium fluoride (TBAF, Scheme 1).[10] In this case, BDMS oxidation was compatible with our hydrosilylation conditions and could be performed directly as a one-pot operation to afford regioselective hydrolysis of the alkyne, whereby **4** was obtained directly from **2** in 88% yield.



Scheme 1. Hydrosilylation–oxidation protocol for propargylic alcohols. a) 1. BDMS-H, 5% **1**, CH_2Cl_2, 0°C to RT, 2. TBAF, then H_2O_2, MeOH, $KHCO_3$; b) octyne, *n*BuLi, $(iPrO)_3TiCl$, −78°C, then **5**; c) 1. BDMS-H, cat. **1** (2% for **9**, **13**, **17**; 3% for **6**), acetone, 0°C to RT, 2. TBAF, then H_2O_2, MeOH, $KHCO_3$; d) 5-phenyl-1-pentyne, *n*BuLi, $ZnBr_2$, −78°C, then **8**; e) 0.20 equiv $Zn(OTf)_2$, 0.22 equiv (+)-*N*-methylephedrine, Et_3N, PhMe, 60°C. RT = room temperature.

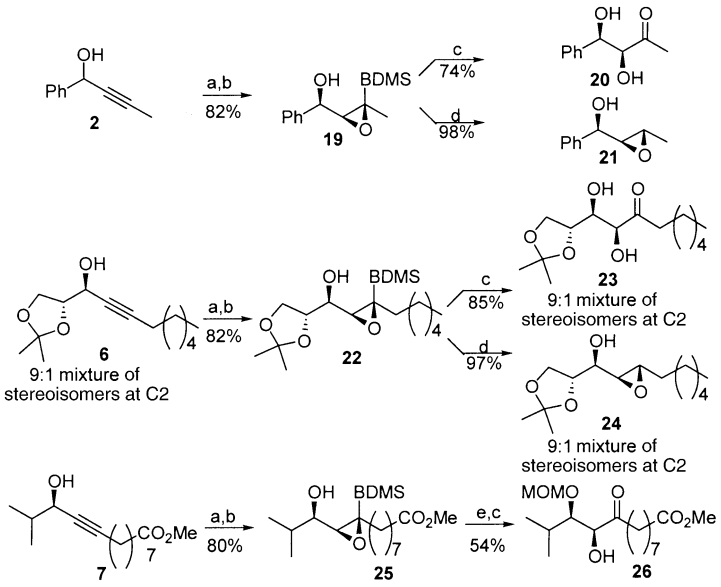
The net diasteroselective aldol requires a diastereoselective addition of an acetylide ion to a chiral aldehyde. Thus, a Felkin–Anh addition of a titanium acetylide complex[11] converts aldehyde **5** into the *anti* adduct **6** with a diastereomer ratio of 9:1. On the other hand, a chelation-controlled addition to the α-alkoxy aldehyde **8** using zinc bromide[12] provides the *syn* adduct **9** (10:1 d.r.). In both cases one-pot hydrosilylation followed by oxidation unmasks the aldol adducts **7** and **10**. Chiral propargylic alcohols can be synthesized readily by the asymmetric hydrogenation of ketones or addition to aldehydes.[3,4] Addition to aldehydes **11** and **15** produced their respective alcohols **13** and **17** in 94% and 85% *ee*, respectively.[4] One-pot hydrosilylation/oxidative desilylation gave the corresponding aldols **14** and **18** in high enantioselectivity in a two-pot sequence.

Additional complexity can be introduced through epoxidation of the vinylsilane. The bulky (*Z*)-silyl group serves as an excellent diastereocontrol element to provide *syn*-epoxides for what is otherwise a challenging class for diastereoselective epoxidation (Scheme 2).[13] Protodesilylation of **19** and **22** provides the respective *syn*-epoxy alcohols **21** and **24** with high efficiency and with a facial selectivity of >20:1. Owing to the BDMS group, oxidation provides α,β-dihydroxyketones **20** and **23** of defined relative and absolute stereochemistry.[14] The added alkyne unit functions as a hydroxymethyl ketone equivalent, and the hydroxy and ketone groups are unmasked simultaneously. Attempts to carry out this process in one or two pots without purification of the intermediates resulted in significantly lower yields. Since the amount of TBAF in the oxidation step is crucial to good yields, the epoxide was best fully purified prior to oxidation. Finally, differentiated diols could be produced by protection of the alcohol prior to epoxidation, though in this case the oxidation (**25**→**26**) was less efficient and accompanied by significant protodesilylation, which accounts for the lower yield of **26.**

The regioselective hydrosilylation presented here allows for the selective functionalization of propargylic alcohols. Focusing on oxidative pathways, we show that the alkyne added can serve as a methyl ketone enolate or hydroxymethyl–ketone–enolate equivalent.

Experimental Section

Typical procedure for the hydrosilylation of propargylic alcohols: Preparation of vinylsilane **3**: 1-Phenyl-2-propyn-1-ol (500 mg, 3.42 mmol) and benzyldimethylsilane (0.591 mL, 4.10 mmol) were taken up in acetone (7.0 mL) under Ar at 0°C. Solid **1** (35 mg,



Scheme 2. Elaboration of silanes by diastereoselective epoxidation. a) BDMS-H, 2% **1**, acetone, 0°C to RT; b) *m*CPBA, CH_2Cl_2, 0°C; c) 1 equiv TBAF, THF, −10°C, then H_2O_2, MeOH, $KHCO_3$, RT; d) TBAF, DMF, RT; e) MOM-Cl, pyr., DCM, 0°C to RT. DCM = dichloromethane, *m*CPBA = *m*-chloroperbenzoic acid, MOM = methoxymethyl, pyr. = pyridine.

0.069 mmol) was added, and the solution was allowed to warm to room temperature and stirred for 30 min. The crude reaction mixture was concentrated directly under reduced pressure and applied to a silica gel column (eluent: petroleum ether/diethyl ether 6:1). The minor olefin regioisomers could be separated to afford the desired vinylsilane (920 mg, 91% yield).

Typical procedure for the one-pot hydrosilylation/oxidation to afford β-hydroxy ketones: Preparation of ketone **18**: To a solution of propargylic alcohol **17** (118 mg, 0.40 mmol) and benzyldimethylsilane (83 μL, 0.48 mmol) in acetone (0.8 mL) was added solid **1** (4.0 mg, 0.008 mmol) at 0°C. The solution was allowed to warm to room temperature and stirred for 30 min. The solution was cooled again to 0°C and treated with THF (1.0 mL) followed by TBAF (0.48 mL, 0.58 mmol, 1M in THF). The reaction mixture was stirred for 15 min, then 30% aqueous H_2O_2 (1.9 mL, 10.7 mmol), MeOH (0.7 mL), and $KHCO_3$ (176 mg, 1.76 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Water (20 mL) was added and the mixture extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and dried over Na_2SO_4. The crude product was applied to a silica gel column (eluent: petroleum ether/ethyl acetate/methanol 80:20:1 then 70:30:1) to afford the desired hydroxyketone as a clear, colorless oil (97 mg, 78% yield).

Typical procedure for the production of dihydroxyketones: preparation of ketone **20**: Vinylsilane **3** (650 mg, 2.19 mmol) was taken up in CH_2Cl_2 (20 mL) and treated with *m*CPBA (662 mg, 3.07 mmol assuming 80% purity) at 0°C. After the reaction mixture had been stirred 14 h, saturated aqueous sodium bicarbonate (10 mL) and solid $Na_2S_2O_3$ (ca. 2 g) were added. The mixture was extracted with ether (3 × 30 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (eluent: petroleum ether/ethyl acetate/methanol 100:10:1) afforded the desired epoxyalcohol as a single isomer (615 mg, 90% yield). Epoxysilane **19** (59 mg, 0.19 mmol) was taken up in THF (0.6 mL) under Ar at 0°C. TBAF (0.19 mL, 0.19 mmol, 1.0M in THF) was added dropwise, and after 5 min, methanol (0.60 mL) and $KHCO_3$ (60 mg, 0.60 mmol) were added, followed by 30% aqueous H_2O_2 (0.20 mL). The mixture was then allowed to warm to room temperature. After 14 h, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification on a silica gel column (eluent: petroleum ether/ethyl acetate 4:1 then 1:1) afforded the desired diol as a viscous gum (25.1 mg, 74% yield).

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Keywords: aldol products · asymmetric synthesis · hydrosilylation · organosilanes · ruthenium catalysis

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