

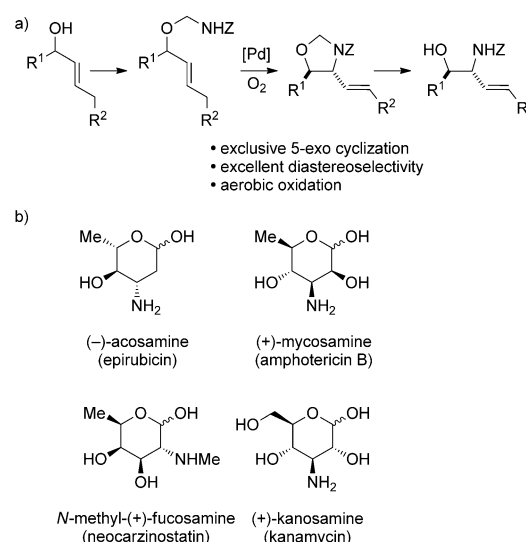
Synthetic Methods

Synthesis of Vicinal Aminoalcohols by Stereoselective Aza-Wacker Cyclizations: Access to (–)-Acosamine by Redox Relay**

Adam B. Weinstein, David P. Schuman, Zhi Xu Tan, and Shannon S. Stahl*

The stereoselective synthesis of vicinal aminoalcohols from simple starting materials is a prominent challenge in organic chemistry. The prevalence of the vicinal aminoalcohol moiety in biologically active molecules, as well as the challenge in accessing the 1,2-oxidation pattern, has justified the development of a diverse array of synthetic approaches to this functionality.^[1] Intermolecular oxidative difunctionalization of alkenes is an appealing strategy for the generation of the 1,2-aminoxylation pattern, but methods with a combination of high stereo- and regioselectivity, and diverse scope remain elusive. Examples include Sharpless asymmetric aminohydroxylation,^[2] metal-catalyzed activation of oxaziridines,^[3] and palladium-catalyzed aminoacetoxylation reactions which employ hypervalent iodine oxidants.^[4] Our interest in palladium-catalyzed aerobic oxidation of alkenes (Wacker-type reactions) prompted us to investigate new methods for the synthesis of vicinal aminoalcohols from readily available, stereochemically defined starting materials. Herein, we employ a detachable, tethered nitrogen nucleophile to generate the 1,2-aminoxylation pattern from allylic alcohols by an aza-Wacker cyclization (Scheme 1 a).^[5–7] The cyclization step forms five-membered oxazolidine products and exhibits high levels of diastereoselectivity. This strategy is amenable to the de novo synthesis of aminosugars, which are key substructures of several antibiotic and anticancer natural products (Scheme 1 b).^[8] Implementation of a redox-relay approach^[9] enables rapid synthesis of (–)-acosamine and highlights the utility of this method.

We began our studies with an assessment of the reactivity and diastereoselectivity of the Wacker cyclization when using distinct tethering units for the attachment of oxygen or nitrogen nucleophiles to secondary allylic amine or allylic alcohol substrates (Table 1). These efforts included the allylic *N*-tosyl carbamate **1** (entries 1–3) and *N*-allyl hemiaminal **3** (entries 4–6) substrates, which were reported previously by Bäckvall and co-workers^[5f] and Hiemstra and co-workers,^[5a] as well as the *O*-allyl hemiaminal **5a**. Assessment of a variety of catalyst conditions for aerobic oxidative cyclization



Scheme 1. a) Detachable tethered nucleophile approach for the synthesis of vicinal aminoalcohols from allylic alcohols. b) Aminosugars in natural product antibiotic and anticancer agents. Z = benzyloxycarbonyl (Cbz) or *tert*-butoxycarbonyl (Boc).

Table 1: Evaluation of diastereoselective oxidative cyclization of substrates derived from an allylic alcohol or an allylic amine.

Entry	Substrate	Major product	Cond. ^[a]	Yield [%]	d.r. ^[b]
1			A	0	n.d.
2			B	11	3.5:1 ^[c]
3			C	0	n.d.
4			A	34	1.6:1
5			B	51	1.6:1
6			C	67	1.8:1
7			A	93	9:1
8			B	94	8:1
9			C	77	5:1

[a] Catalyst conditions A: 5 mol % Pd(TFA)₂, 20 mol % DMSO, 20 mol % NaOBz, 3 Å M.S., THF (0.1 M), 25 °C, 24 h, 1 atm O₂. Catalyst conditions B: 5 mol % Pd(TFA)₂, 20 mol % NaOBz, 3 Å M.S., DMSO (0.1 M), 60 °C, 24 h, 1 atm O₂. Catalyst conditions C: 5 mol % Pd(OAc)₂, DMSO (0.1 M), 60 °C, 24 h, 1 atm O₂. [b] Yield/diastereomeric ratio based on ¹H NMR spectroscopic analysis of the crude reaction mixture with phenyltrimethylsilane as the internal standard. [c] Yield of the isolated product. Diastereomeric ratio based on ¹H NMR analysis of the purified products. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Cbz = benzyloxycarbonyl, DMSO = dimethylsulfoxide, M.S. = molecular sieves, THF = tetrahydrofuran, TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.

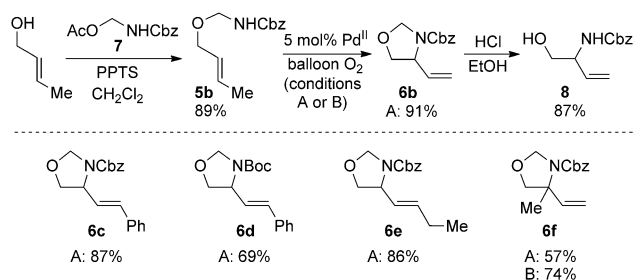
[*] A. B. Weinstein, D. P. Schuman, Z. X. Tan, Prof. S. S. Stahl
Department of Chemistry, University of Wisconsin-Madison
1101 University Avenue, Madison, WI 53706 (USA)
E-mail: stahl@chem.wisc.edu
Homepage: stahl.chem.wisc.edu

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revealed palladium(II)/dimethylsulfoxide-based catalysts to be the most promising.^[10] Effective catalyst systems included [Pd(DMSO)₂(TFA)₂] in THF,^[10c] which is effective at ambient temperatures (conditions A), Pd(TFA)₂ in DMSO, which is compatible with higher reaction temperatures (conditions B), and Pd(OAc)₂ in DMSO, which resemble conditions originally discovered by Larock and Hightower^[10a] and Hiemstra and co-workers^[10b] (conditions C). The allylic *N*-tosyl carbamate substrate **1** was susceptible to decomposition under these direct aerobic reoxidation conditions.^[11] When cyclization to the oxazolidinone **2** occurred (e.g., entry 2), only modest diastereoselectivity was observed. The *N*-allyl hemiaminal **3** cyclized to the corresponding oxazolidine **4** in moderate yields, but the diastereoselectivity of the transformation was poor.^[12] *O*-Allyl hemiaminals are an appealing class of substrates because they may be synthesized directly from allylic alcohols, but they have not been tested previously in Wacker-type cyclizations. The benzyl carbamate (Cbz) derivative **5a** underwent cyclization in excellent yield and good diastereoselectivity to afford the *trans*-oxazolidine **6a** (entries 7–9). Conditions A and B were particularly effective.

The three-step detachable tethered nucleophile approach for the conversion of a *trans*-crotyl alcohol into the vicinal aminoalcohol derivative **8** is illustrated in Scheme 2. *Trans*-crotyl alcohol is readily converted into the corresponding *O*-allyl hemiaminal, and aza-Wacker cyclization proceeds



Scheme 2. Transformation of primary allylic alcohols into vicinal aminoalcohols. PPTS = pyridinium *p*-toluenesulfonate.

smoothly at ambient temperature (condition A). The oxazolidine ring is unmasked under acidic conditions. Several additional primary *O*-allyl hemiaminal substrates were similarly effective. Comparison of benzyl- (Cbz) and *tert*-butyl carbamate (Boc) *O*-allyl hemiaminals revealed that the Cbz-derived nitrogen nucleophile is more effective (**6c** versus **6d**). A propyl-substituted alkene produced the oxazolidine **6e** with negligible alkene isomerization.^[13] Finally, reaction with a trisubstituted alkene affords a tertiary C–N bond (**6f**); conditions B was more effective than condition A in this reaction.

We next explored the scope of the diastereoselective cyclization of *O*-allyl hemiaminals derived from secondary alcohols (Table 2). Both *trans*- and *cis*-allylic alcohols are good substrates and afford the same *trans*-4,5-disubstituted oxazolidine (entries 2 and 3). The effectiveness of the *trans*-allylic alcohol substrate is noteworthy because such substrates are more readily accessible than the *cis* analogue. However,

Table 2: Diastereoselective synthesis of oxazolidines from cyclization of secondary *O*-allyl hemiaminals.

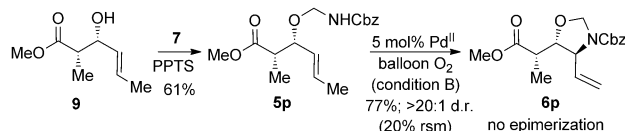
Entry	Substrate	Product	Cond. ^[a]	Yield [%]	d.r. ^[b]
1			A	86	12:1
2			B	88	11:1
3			B	73	> 20:1
4			A	72	> 20:1
5			B	85	> 20:1
6			B	75	> 20:1
7			B	78	> 20:1
8			B	59	> 20:1
9			B	53	> 20:1
10			B	62	9:1
11			B	74	19:1
12			B	75	9:1

[a] See Table 1 for descriptions of catalyst conditions A and B. [b] Yields of the isolated products. Diastereomeric ratio based on ¹H NMR spectroscopic analysis of the isolated material. Relative configurations of **6a** and **6j** were assigned by NOESY-1D spectroscopic analysis (other structures assigned by analogy).

higher diastereoselectivity can be achieved with the *cis* substrate. Increasing the size of the secondary allylic substituent improves the diastereoselectivity, and conditions B provides higher reactivity with these more sterically encumbered substrates (entries 4–6). The cyclic *O*-allyl hemiaminals **5j** and **5k** yield the *cis*-ring-fused products in good yields (entries 7 and 8). Allylic alcohols derived from aldol additions to crotonaldehyde also provide effective *O*-allyl hemiaminal

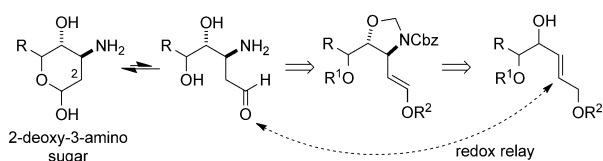
substrates (entries 9–12). The ketone adduct **5l** is prone to decomposition under the reaction conditions and provides only modest yield of the oxazolidine **6l**, but the Weinreb amide **5m**, ethyl ester **5n**, and dimethylamide **5o** are well-tolerated.

The aldol reaction is one of many potential routes to enantioenriched allylic alcohols^[14] and thus can provide access to enantioenriched aminoalcohol derivatives in connection with our method. An asymmetric aldol reaction enabled the synthesis of the enantioenriched allylic alcohol **9** from crotonaldehyde,^[15] which was converted into the corresponding *O*-allyl hemiaminal **5p** and cyclized cleanly to the oxazolidine **6p** (Scheme 3). The oxazolidine **6p** was obtained with exquisite diastereoselectivity and no epimerization of the α -methyl stereocenter.



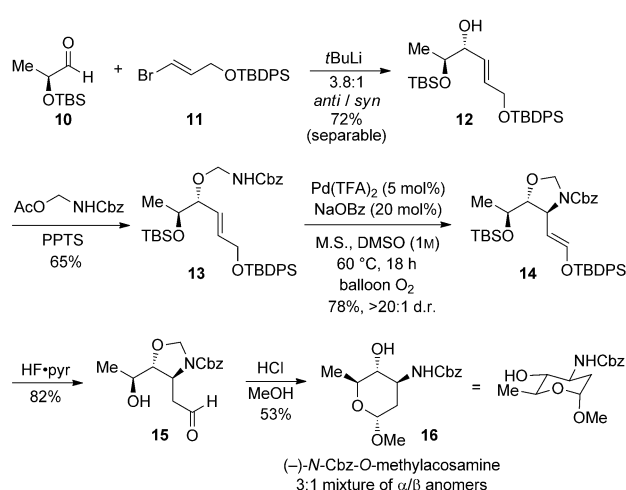
Scheme 3. Transformation of enantioenriched allylic alcohol to the oxazolidine with no epimerization. rsm = recovered starting material.

The utility of this method is illustrated in the synthesis of the 2-deoxy-3-aminosugar (–)-acosamine.^[16] 2-Deoxy-3-aminosugars can be obtained by synthesis of the corresponding acyclic 1,3-aminoaldehyde precursor. We envisioned that the aminoaldehyde could be accessed rapidly by employing our cyclization in a redox-relay sequence, whereby cyclization of an *O*-allyl hemiaminal derived from a bis(allylic alcohol) precursor would generate a masked aldehyde intermediate (Scheme 4). Transfer of the olefin redox equivalent by β -hydride elimination from the second allylic alcohol position would form an enol ether and expedite elaboration of the oxazolidine to the desired aminosugar target.



Scheme 4. Retrosynthetic analysis of 2-deoxy-3-aminosugars with application of aza-Wacker cyclization and redox-relay.

This redox-relay strategy enabled the synthesis of (–)-*N*-Cbz-*O*-methylacosamine, a conveniently isolated derivative of acosamine, from TBS-protected (–)-lactaldehyde in five steps (Scheme 5). First, vinylolithium addition of the silyl-protected allylic alcohol **11** to the lactaldehyde **10** yielded **12** with the desired stereochemistry. Installation of the *O*-allyl hemiaminal and aza-Wacker cyclization provided the silyl enol ether **14** with good efficiency as a single diastereomer.^[17] The silyl enol ether and secondary TBS ether were removed to unveil the free aldehyde and alcohol. Finally, the oxazo-



Scheme 5. Synthesis of (–)-*N*-Cbz-*O*-methylacosamine. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

lidine ring was opened under acidic conditions with concomitant formation of the methyl-protected cyclic acetal **16** [(–)-*N*-Cbz-*O*-methylacosamine]. This rapid and redox economical synthesis of (–)-acosamine illustrates a versatile approach which could be applied to a variety of other aminosugar derivatives.

In summary, we have demonstrated that aza-Wacker cyclizations can be used to synthesize stereodefined vicinal aminoalcohols from allylic alcohol precursors by employing a detachable tethered nucleophile approach. These oxidative functionalization reactions are operationally simple and the catalytic reactions give clean conversion of starting material into desired product. The diversity of methods for the asymmetric synthesis of allylic alcohols makes the diastereoselective transformation described here particularly apt for application to a variety of contexts.

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