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

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Abstract

Diastereoselective aza-Wacker cyclization of O-allyl hemiaminals under aerobic conditions enables efficient access to 1,2-aminoalcohol derivatives from allylic alcohols. The scope of this method is presented and its utility is highlighted in a streamlined synthesis of the biologically important aminosugar (–)-acosamine.

Keywords

palladium; oxidation; stereoselective catalysis; amination; Wacker oxidation; organic synthesis

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 difficulty with which the 1,2-oxidation pattern can be synthesized, has justified the development of a diverse array of approaches to access these molecules.^[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 that employ hypervalent iodine oxidants.^[4] Our interest in palladium-catalyzed *aerobic* oxidation of alkenes (Wacker-type reactions) prompted us to investigate new methods for

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the synthesis of vicinal aminoalcohols from readily available, stereochemically defined starting materials. Here, we employ a detachable, tethered nitrogen nucleophile to generate the 1,2-aminoxygenation pattern from allylic alcohols via an aza-Wacker cyclization (Scheme 1a).^[5, 6, 7] The cyclization step forms 5-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 1b).^[8] Implementation of a redox-relay approach⁹ 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 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, reported previously by Bäckvall^[5f] and Hiemstra,^[5a] as well as aminal **5a**. Assessment of a variety of catalyst conditions for aerobic oxidative cyclization revealed Pd^{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 temperature (condition **A**), Pd(TFA)₂ in DMSO, which is compatible with higher reaction temperatures (condition **B**), and Pd(OAc)₂ in DMSO, resembling conditions originally discovered by Larock^[10a] and Hiemstra^[10b] (condition **C**). Allylic *N*-tosyl carbamate substrate **1** was susceptible to decomposition under these direct aerobic reoxidation conditions.^[11] When cyclization to oxazolidinone **2** occurred (e.g., entry 2), only modest diastereoselectivity was observed. *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 *trans* crotyl alcohol to vicinal aminoalcohol derivative **8** is illustrated in Scheme 2. *Trans*-crotyl alcohol is readily converted to the corresponding *O*-allyl hemiaminal, and aza-Wacker cyclization proceeds 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 and *tert*-butyl carbamate (Cbz- and Boc-) *O*-allyl hemiaminals revealed that the Cbz-derived nitrogen nucleophile is more effective (cf. **6c** and **6d**). A propyl-substituted alkene produced oxazolidine **6e** with negligible alkene isomerization.^[13] Finally, reaction with a trisubstituted alkene affords a tertiary C–N bond (cf. **6f**); condition **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 2-3). The effectiveness of the *trans*-allylic alcohol substrate is noteworthy because such substrates are more readily accessible than the *cis* analog; however, higher diastereoselectivity can be achieved with the *cis* substrate. Increasing the size of the secondary allylic substituent improves the diastereoselectivity, and condition **B** provides higher reactivity with these more sterically encumbered substrates (entries 4-6). Cyclic *O*-allyl hemiaminals **5j** and **5k** yield the *cis* ring-fused products in good yields (entries 7-8). Allylic alcohols derived from aldol additions to crotonaldehyde also provide effective *O*-allyl hemiaminal substrates (entries 9-12). Ketone adduct **5l** is prone to decomposition under the reaction conditions and

provided only modest yield of 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. Asymmetric aldol chemistry enabled the synthesis of enantioenriched allylic alcohol **9** from crotonaldehyde,^[15] which was converted to the corresponding *O*-allyl hemiaminal **5p** and cyclized cleanly to oxazolidine **6p** (Scheme 3). Oxazolidine **6p** was obtained with exquisite diastereoselectivity and no epimerization of the α methyl stereocenter.

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 via 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 via 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.

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 silyl-protected allylic alcohol **11** to 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 oxazolidine 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 that 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 to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

a) Detachable tethered nucleophile approach for the synthesis of vicinal aminoalcohols from allylic alcohols and b) aminosugars in natural product antibiotic and anticancer agents.

Scheme 2.

Transformation of primary allylic alcohols to vicinal aminoalcohols. (PPTS = pyridinium *p*-toluenesulfonate)

Scheme 3.

Transformation of enantioenriched allylic alcohol to the oxazolidine with no epimerization.

Scheme 4.

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

Scheme 5.
 Synthesis of (-)-N-Cbz-O-methylacosamine

Table 1

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

entry	substrate	major product	conditions ^[a]	yield (%) / d.r. ^[b]
1			A	0 / nd
2			B	11 / 3.5:1 ^[c]
3			C	0 / nd
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 condition 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 condition 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 condition 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] Isolated yield. Diastereomeric ratio based on ¹H NMR analysis of the purified products.

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

entry	substrate	product	conditions ^[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

entry	substrate	product	conditions ^[a]	yield (%) / d.r. ^[b]
11	5n	6n	B	74 / 19:1
12	5o	6o	B	75 / 9:1

^[a] See Table 1 for descriptions of catalyst conditions **A** and **B**.

^[b] Isolated yields. 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).