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N,O-Heterocycles as synthetic intermediates*

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Abstract: Hydroxylamines can be cyclized under various conditions according to the nature of the unsaturation in the *N*-substituent. Both isoxazolidines and tetrahydrooxazines can be formed with good synthetic control. The choice of the appropriate cyclization reaction leads to syntheses of the natural products sedamine and monomorine. The related *N*,*O*-acetals are shown to undergo efficient ring-opening under Sakurai conditions.

Keywords: hydroxylamines; isoxazolidines; tetrahydrooxazines; sedamine; monomorine; Sakurai conditions; cyclization.

We have been interested in two classes of *N*,*O*-heterocycles. The first class contains a direct *N*,*O*-bond. Our interest in these was as intermediates for the synthesis of amino alcohols with control of the regio- and stereochemistry. Thus, we intended to employ the hydroxylamine as a form of tethered nitrogen while inducing ring closure onto an alkene. This might lead to either isoxazolidines or oxazines. Our hope was to develop new routes to these heterocycles that would complement the existing routes based on cycloaddition chemistry.

The idea of using a tethered nitrogen—a nitrogen atom temporarily connected to another functional group—to overcome problems of regioselectivity, stereoselectivity, chemoselectivity, and just simple reactivity, is not new. Knapp has reviewed his own elegant contributions to this area, especially in the area of amino sugar analogs [1]. Hirama and Ito have also reviewed their own work [2]. The difficulty arises with the choice of tether. An obvious choice is to use a carbonyl group to tether the desired nitrogen to a pre-existing oxygen. Such carbamates can be easily prepared, but when used often react via oxygen, rather than nitrogen. Knapp's solution to this problem was to modify the carbonyl structure to ensure that nucleophilicity remained with the nitrogen. Ito and Hirama employed a *N*-tosyl group so that a nitrogen-centered anion could easily be generated. Although ingenious, both of these solutions either add steps or decrease atom efficiency. In search of a simpler tether, we turned to hydroxylamines, in which the tether would be just a N–O single bond. That part of the procedure, at least, could not be more atom economical. An important consideration was to be able to cleave the tether, the N–O bond, selectively under mild conditions. Fortunately, hydroxylamines can be reduced under various conditions, including catalytic hydrogenolysis, dissolving metals, and even by hydride nucleophiles, although this last set of conditions usually requires some forcing. Other groups have also

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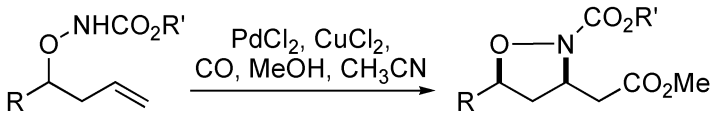
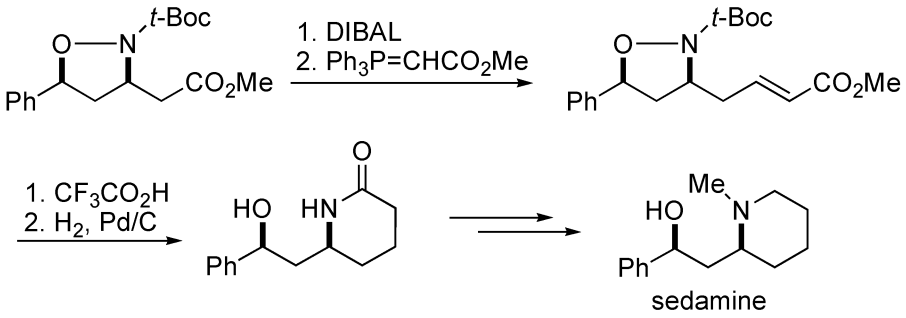
hit upon this strategy, but used electrophilic triggers from the p-block, rather than the organometallic systems that we had in mind [3].

Our first foray into the field was designed to exploit palladium(II)-induced ring-closing onto an alkene, with subsequent CO insertion leading to a useful ester group (Scheme 1) [4]. This approach was based on the work of several authors who employed alcohols as the intramolecular nucleophile [5]. The starting materials proved to be very easy to make. Homoallylic alcohols could be converted into *N*-phthaloyl hydroxylamines using Mitsunobu chemistry [6] due to the surprisingly high acidity of *N*-hydroxyphthalimide. Deprotection, in typical Ing–Manske style using hydrazine, proved remarkably facile, going to completion in minutes at room temperature. The N-unsubstituted hydroxylamines failed to react under the palladium-catalyzed carbonylation conditions, but the corresponding carbamates cyclized efficiently and with complete stereoselectivity. Even so, we were only able to prepare five-membered rings in this way.



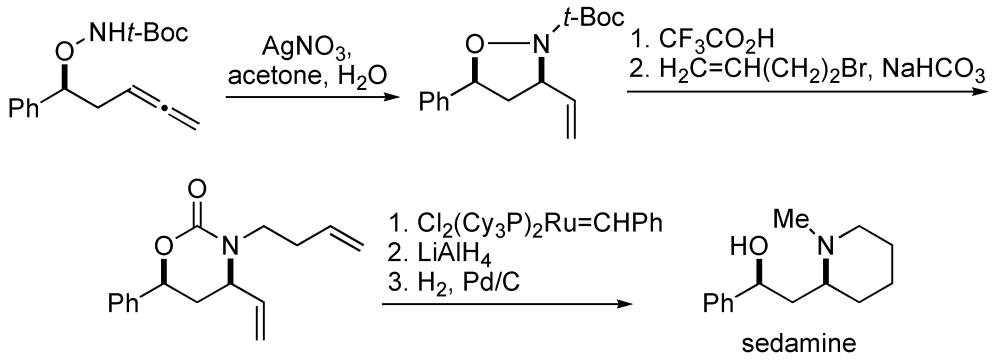
Scheme 1 Palladium-catalyzed isoxazolidine synthesis.

With the methodology in hand, we approached the synthesis of sedamine (Scheme 2) [7]. Using the appropriate isoxazolidine, prepared in optically active fashion by asymmetric allylation of benzaldehyde, we were able to install the additional carbon atoms by a reduction-Wittig sequence. A tandem double hydrogenation–lactamization then yielded a hydroxy lactam as a single isomer. This compound was then carried through to sedamine using simple manipulations.



Scheme 2 Synthesis of sedamine.

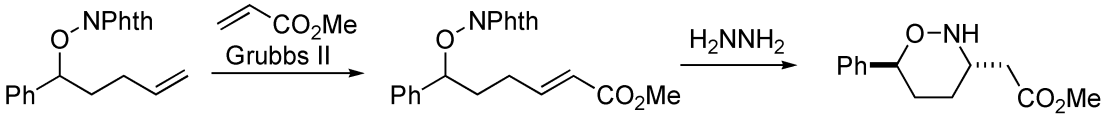
The disadvantage of this reaction is the requirement to employ an excess of the oxidizing agent that is required to bring the palladium back up to its +2 oxidation state in the catalytic cycle. We turned to the Claesson cyclization of allenes using silver(I) as an alternative method [8]. Gratifyingly, the allenes underwent cyclization under mild conditions to yield vinyl isoxazolidines (Scheme 3) [9]. Although the stereoselectivity was lower than in the palladium chemistry, it remained at useful levels. Again, one of the products could be taken through to sedamine, this time using a ring-closing metathesis (RCM) to form the piperidine ring. A prerequisite to the RCM is the installation of the butenyl side chain. This proved a little troublesome and required considerable optimization. In this case, involving a primary alkyl bromide, useful yields could be obtained, but subsequent experiments with secondary halides and mesylates have been uniformly disapppointing. Curiously, in the presence of the hydroxyl-



Scheme 3 Second synthesis of sedamine.

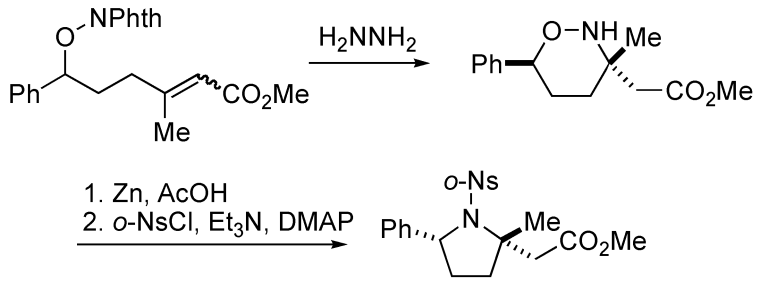
amine group, RCM failed [10]. RCM still failed even after quaternization of the nitrogen. This problem was solved by cleaving the N–O bond and protecting the product as a cyclic carbamate.

Our third system involves Michael addition (Scheme 4). We speculated that the same compounds that we employed in the palladium chemistry, with a *t*-Boc protected hydroxylamine, as well as their higher homologs, could undergo cross-metathesis with electron-poor alkenes, such as methyl acrylate, followed by subsequent intramolecular conjugate addition. Unfortunately, the cross-metathesis was complicated by attack on the N–O bond by ruthenium, resulting in low yields of the desired cross-metathesis product, catalyst deactivation, and, in one case, isolation of a curious ketone. In complete contrast, cross-metathesis of the phthaloyl-protected hydroxylamines proceeded very efficiently, even with only 0.5 mole % of Grubbs second-generation catalyst. Subsequent dephthaloylation resulted in tandem intramolecular Michael addition to give isoxazolidines with poor stereoselectivity and tetrahydro-[1,2]-oxazines selectively as their *trans*-isomers [11].



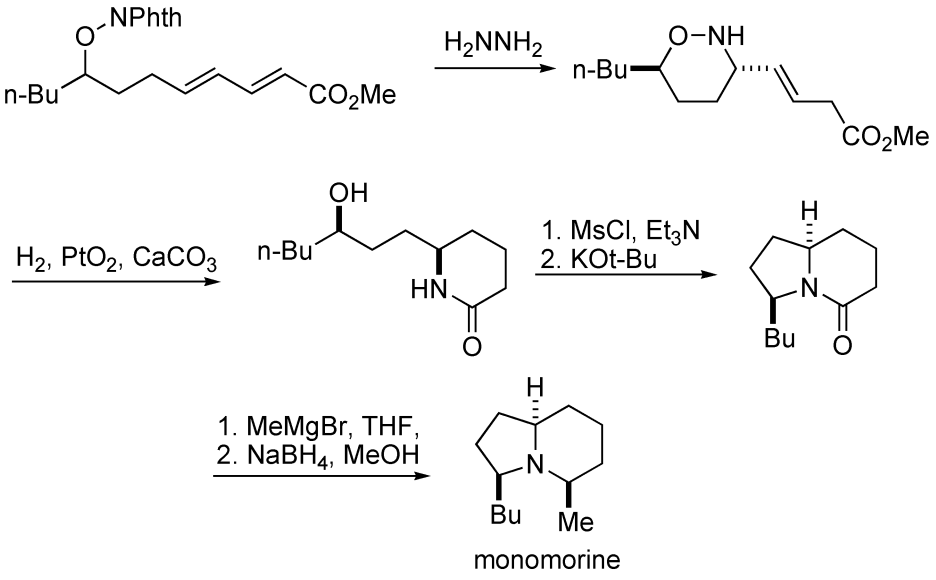
Scheme 4 The metathesis-Michael approach.

The intramolecular Michael addition is completely stereoselective even when a trisubstituted alkene is involved, leading to the creation of a quaternary center (Scheme 5). In this case, we had to convert the oxazine to a pyrrolidine in order to determine the stereochemistry by X-ray crystallography.



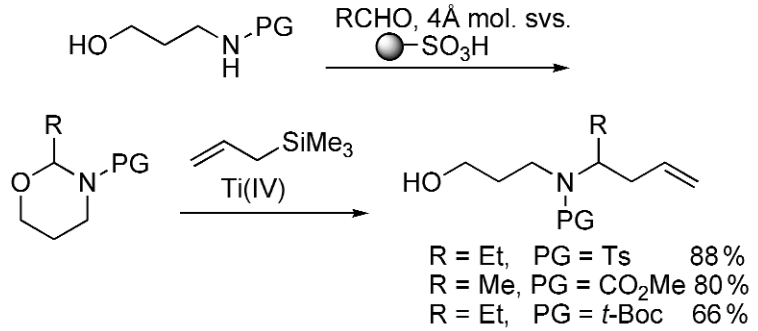
Scheme 5 Pyrrolidine synthesis.

This chemistry has been employed in a synthesis of monomorine, an indolizidine alkaloid isolated from the pharaoh ant (Scheme 6) [12]. The key steps were an intramolecular 1,6-conjugate addition of a hydroxylamine, followed by a tandem double hydrogenation-cyclization.



Scheme 6 Monomorine synthesis.

Our second class of *N*,*O*-heterocycles are cyclic *N*,*O*-acetals. We have focused on *N*,*O*-acetals in which the nitrogen bears an electron-withdrawing group. Our need for this reaction arose from the failure of isoxazolidines to undergo reaction with secondary alkyl sulfonates, in contrast to the sucessful reaction of primary alkyl halides (Scheme 3). We anticipated that the *N*,*O*-acetals would, under Lewis acidic conditions, open to iminium ions which could be trapped with appropriate nucleophiles [13]. The *N*,*O* acetals are easily prepared from the corresponding N-protected amino alcohols and, in most cases, undergo smooth and clean ring-opening on exposure to allyltrimethylsilane in the presence of a strong Lewis acid, such as $TiCl_4$ or $SnCl_4$ (Scheme 7). In this way, we have been able to create the secondary centers that eluded us during attempted isoxazolidine *N*-alkylation chemistry.



Scheme 7 Synthesis and Sakurai reaction of *N*,*O*-acetals.

This reaction, a variation on the Sakurai reaction [14], is quite general, and works in high yield for acetals derived from alkyl aldehydes, and with a range of standard protection groups, such as tosyl, Cbz, methoxycarbonyl, and even the acid labile *t*-Boc.

The hydroxylamine cyclization chemistry provides an efficent and varied route to amino alcohols with control of the stereochemistry, provided that the right mode of cyclization is selected. The *N*,*O*-acetal chemistry furnishes a convenient way to further functionalize the nitrogen atom. It may be anticipated that this combination of reactions will lead to some further efficient natural product syntheses.

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