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Stereoselective syntheses of heterocycles via metallated alkoxyallenes*

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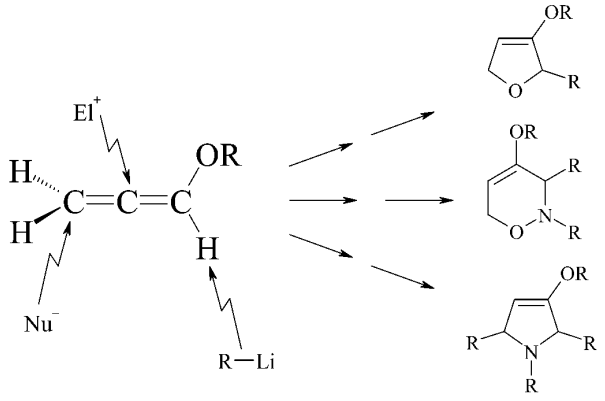
Abstract: *n*-Butyllithium smoothly deprotonates alkoxyallenes at C-1. The generated lithiated species reacts with a variety of electrophiles furnishing after cyclization functionalized furan, pyrrole, or 1,2-oxazine derivatives. The formation of new C–C bonds often occurs with high stereoselectivities, which are exploited for efficient and selective syntheses of natural products or other compounds of interest.

INTRODUCTION

Alkoxyallenes serve as extremely versatile C-3 building blocks for the synthesis of various 5- and 6-membered functionalized heterocycles. This is due to the general reactivity pattern of alkoxyallenes as depicted in Scheme 1. They show normal enol ether reactivity with electrophiles that attack the central carbon, whereas nucleophiles add to the terminal carbon activated by the C–O single bond. Most importantly, substituted alkoxyallenes can be obtained by smooth lithiation of C-1 and subsequent addition of electrophiles to this center. This makes available a large range of substituted alkoxyallene derivatives.



Scheme 1 Reactivity pattern of alkoxyallenes and heterocycles derived thereof.

The straightforward preparation of methoxyallene and the generation of the lithiated species is illustrated in Scheme 2; these procedures go back to Hoff, Brandsma, and Arens [1]. These authors have also reported the first reactions of lithiated methoxyallene, and they could demonstrate that aldehydes

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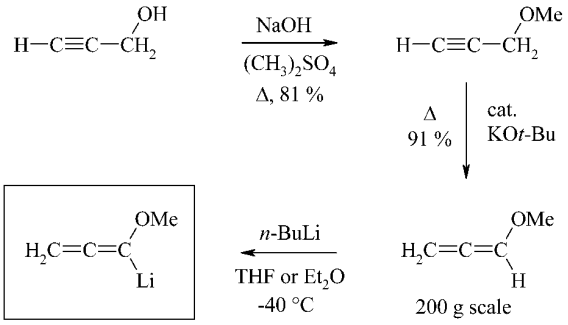
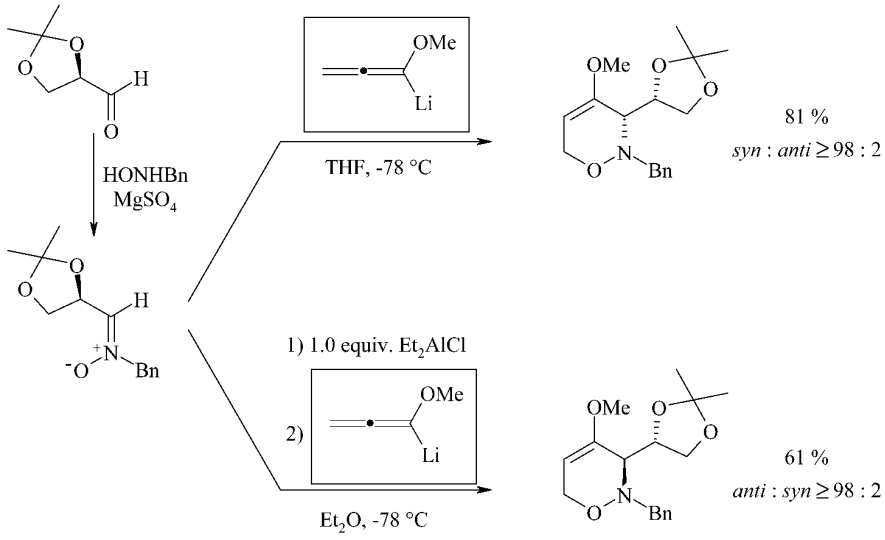
and ketones as electrophiles open an efficient way to dihydrofuran and furanone derivatives [2,3]. We could extend their seminal studies to asymmetric syntheses of these heterocycles, employing suitably protected enantiomerically pure α-amino aldehydes [4]. Interestingly, after transmetallation to the corresponding titanium species, addition of aldehydes occurs at the terminal γ-carbon, providing γ-butyrolactones after acidic workup with high stereoselectivity. By this way, metallated methoxyallene serves as homo esterenolate equivalent [5].



Scheme 2 Generation of lithiated methoxyallene.

RESULTS

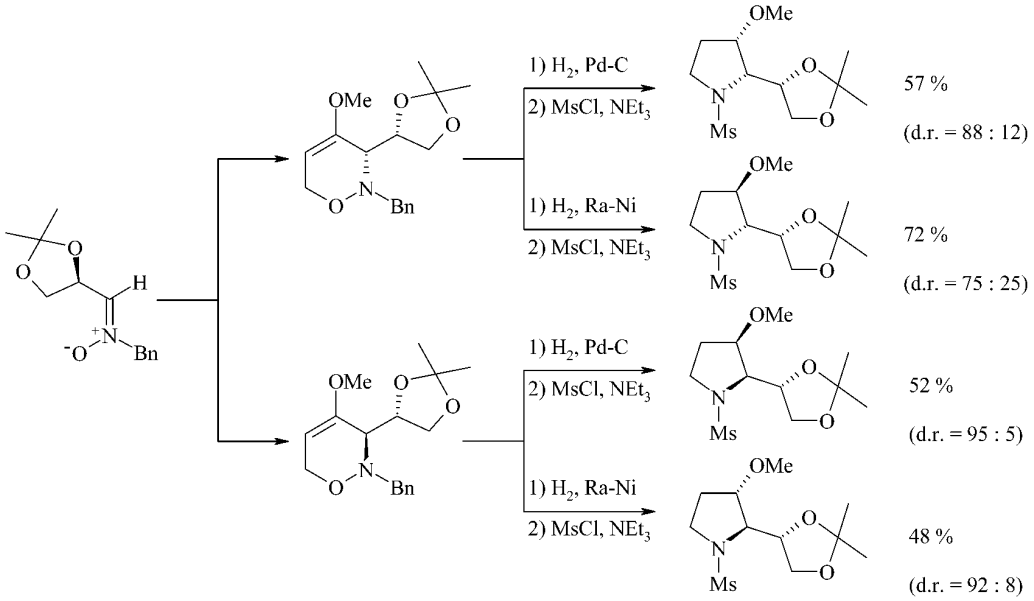
Recently, we started to employ nitrogen-containing electrophiles to try related syntheses of heterocycles with nitrogen. With nitrones as highly reactive imine equivalents [6] we expected the corresponding hydroxylamine derivatives as primary products, however, these could be isolated only in exceptional cases with high steric hindrance. In general, addition of lithiated methoxyallene to nitrones followed by aqueous workup furnished 1,2-oxazine derivatives, which arise by cyclization of the proposed primary adducts [7]. A typical example employing a glyceraldehyde-derived nitrone is depicted in Scheme 3, which also demonstrates that a complete switch in the diastereofacial selectivity can be achieved by precomplexation of the nitrone with diethylaluminum chloride [8]. Other 1,2-oxazines



Scheme 3 Addition of lithiated methoxyallene to a glyceraldehyde-derived nitrone.

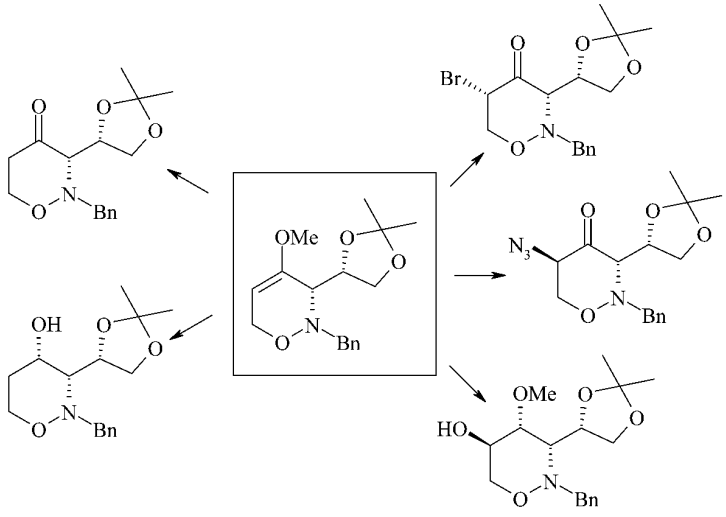
were obtained starting from simple achiral nitrones and from carbohydrate or α-amino aldehyde-derived chiral nitrones.

The two diastereomeric 1,2-oxazines obtained from the glyceraldehyde nitrone are ideal precursors for stereoselective syntheses of amino sugar derivatives and highly substituted pyrrolidines. An example of a stereodivergent synthesis of oxygenated pyrrolidine derivatives is depicted in Scheme 4. The major configuration of the newly generated stereogenic center depends on the catalyst employed in the reduction process. An explanation for this at first glance very surprising behavior is given in our communication [9].



Scheme 4 Stereodivergent synthesis of oxygenated pyrrolidine derivatives.

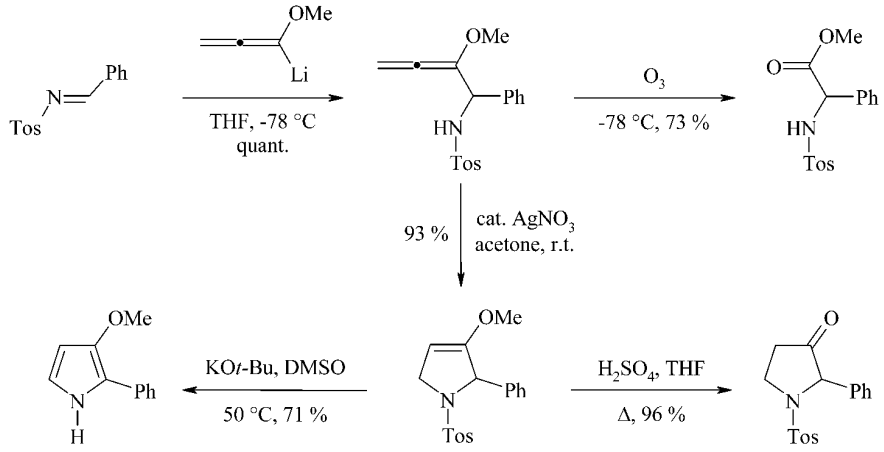
Owing to their enol ether unit, the 1,2-oxazines can further be functionalized and serve as templates for introduction of new functionalities. Scheme 5 collects compounds so far obtained from the



Scheme 5 Compounds derived from glyceraldehyde-derived *syn*-1,2-oxazine.

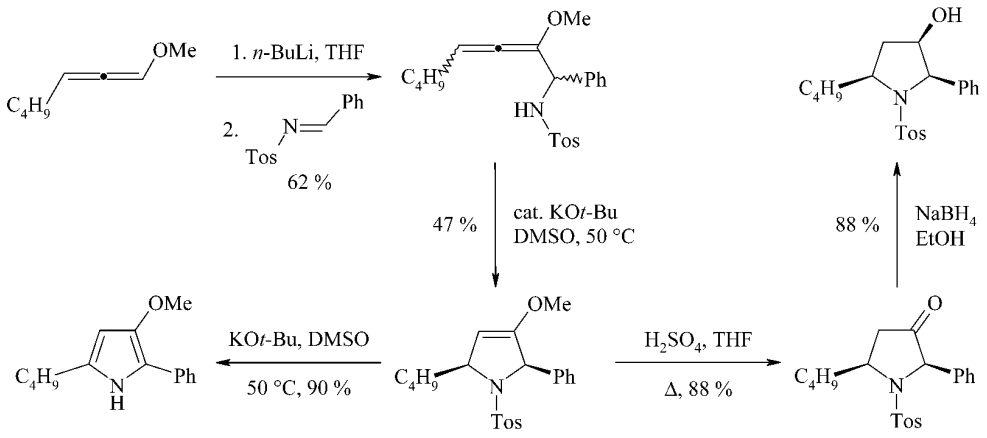
syn-1,2-oxazine. Thus, a range of highly functionalized 1,2-oxazines has been prepared, which may be regarded as azasugars and might have (in their deprotected form) interesting biological activities, e.g., glycosidase inhibitor properties. All these compounds can also serve as precursors of ring-contracted or acyclic products.

The addition of imines to lithiated methoxyallene provided the expected primary allenyl amines in very good yields. Not only the rather reactive *N*-tosyl imines but also *N*-alkyl and *N*-benzyl imines may be efficiently used. The primary adducts can be cyclized to afford dihydropyrrole derivatives either under basic conditions or with the aid of transition-metal catalysts such as silver nitrate or palladium complexes [10]. Scheme 6 illustrates which compounds are derived from an *N*-tosyl imine by various subsequent steps.



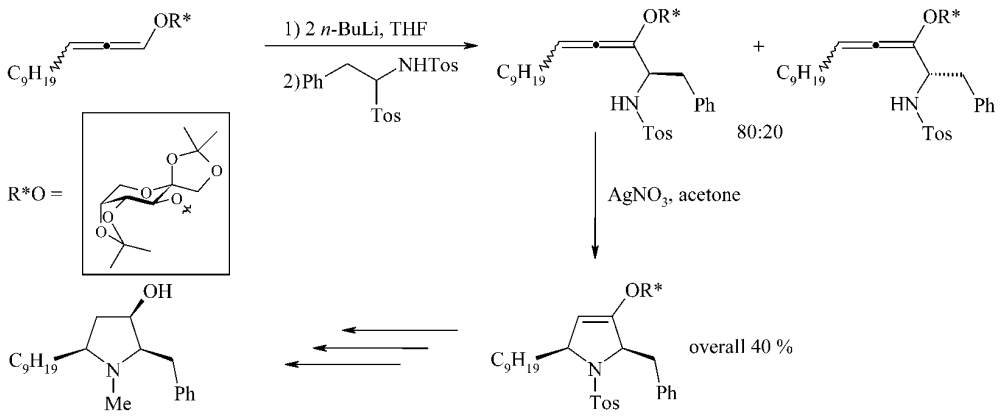
Scheme 6 Synthesis and reactions of an allenyl amine.

The synthesis of dihydropyrrole derivatives is very general and occurs under high stereocontrol if the imine carbon contains inducing α-stereocenters. This allows short and efficient synthesis of pyrrolidinol derivatives. A further extension of our work deals with synthesis and reactions of 3-substituted lithiated alkoxyallenes. The required starting materials were obtained by straightforward procedures, and the additions to imines furnished the expected allenyl imines in good yields. However, no remarkable stereoselectivity was observed with respect to the relation between the axial and the central stereoelements [10]. Nevertheless, this method allows smooth preparation of tetrasubstituted pyrrole derivatives as illustrated in Scheme 7.



Scheme 7 Synthesis and reactions of a 3-substituted allenyl amine.

This methodology was used to prepare the natural product preussin, which is of interest owing to its fungicidal, antibiotic, and cytotoxic activity. After a synthesis of a racemic sample we could achieve the rather efficient preparation of the unnatural enantiomer with the crucial steps being displayed in Scheme 8. As an inducing auxiliary we used a cheap D-fructose derivative that was installed by standard methods [11]. The desired enantiomerically pure 2,5-*cis*-substituted dihydropyrrole derivative could be obtained with reasonable efficiency. Its conversion into (–)-preussin was then completed with a few further steps [12].



Scheme 8 Stereoselective synthesis of enantiomerically pure (–)-preussin.

CONCLUSIONS

The examples shown reveal the extreme versatility of metallated alkoxyallenes in stereoselective syntheses of several types of heterocycles [13]. Extensions of these methods and application of the established procedures to natural product syntheses are apparent and shall be reported in due course.

ACKNOWLEDGMENTS

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