Stereoselective Syntheses of Heterocycles with Lithiated Methoxyallene

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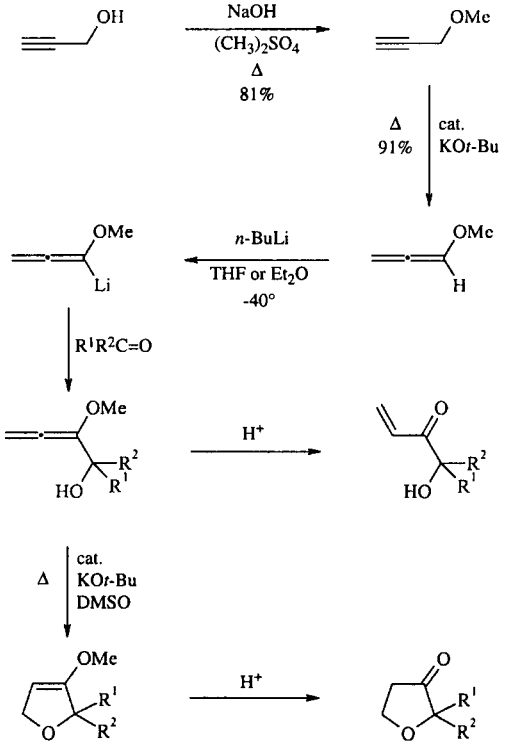
Introduction.

Development of flexible syntheses of heterocycles by building block systems is still a pretentious challenge for organic chemists. Meanwhile, classical condensation reactions are supplemented by cycloadditions as 1,3-dipolar cycloadditions and hetero Diels-Alder reactions. More recently, organometallic reagents had a considerable impact on syntheses of heterocycles, however, most novel methods mainly provide new C-C bonds or functional groups at an existing heterocyclic core. We here report on the formation of heterocycles using a simple three-carbon building block, which after lithiation is combined with various X-Y double bond systems thus affording heterocycles by formal [3 + 2], [3 + 3], or [4 + 1] cyclization processes. Particular emphasis is laid on the stereoselectivity of these reactions and the subsequent elaboration of the heterocyclic compounds obtained for stereocontrolled preparation of cyclic and acyclic target molecules.

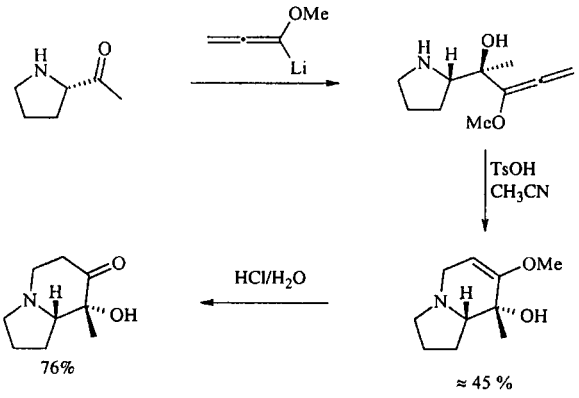
The crucial starting material for the chemistry to be described is methoxyallene which was first prepared by Hoff, Brandsma and Arens in 1968 [1]. The prominent feature [2] of this readily available compound is its smooth metallation by *n*-butyllithium, and the reactions of the corresponding lithiated species with various electrophiles (Scheme 1) [3]. The pioneer work again goes back to the Dutch group who demonstrated that adducts with carbonyl compounds can either be hydrolyzed to enones or transformed into dihydrofuran derivatives and finally to 3(2*H*)-dihydrofuranones [4].

This approach to furanone derivatives was exploited by Magnus and co-workers for synthesis of spiro systems using a repetitive methodology [5]. One example from Overman's group demonstrated that preparation of an indolizinone derivative is also possible if a proline derived amino ketone was used as electrophile (Scheme 2) [6]. This route should have considerable potential for synthesis of enantiopure piperidones.

Scheme 1



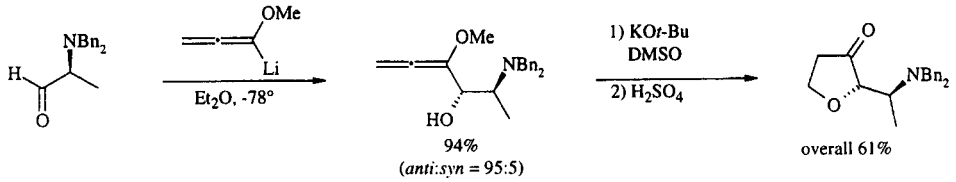
Scheme 2



Results.

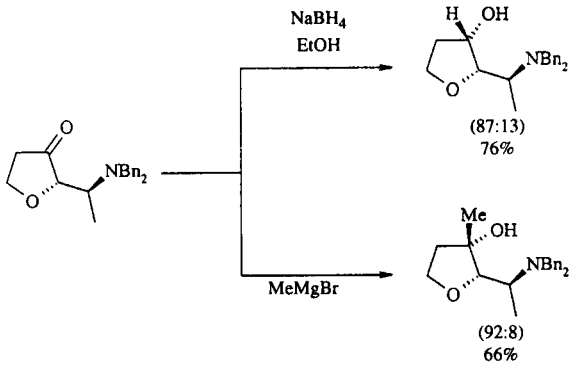
We entered the field since we were interested in the preparation of enantiopure dihydrofuran derivatives [7]. Gratifyingly, optically pure dibenzyl-protected α-amino aldehydes were suitable electrophiles for reactions with lithiated methoxyallene furnishing the expected primary addition products in high anti-diastereoselectivity (Scheme 3). These could be cyclized followed by acidic hydrolysis to give enantiopure furanone derivatives [8,9].

Scheme 3

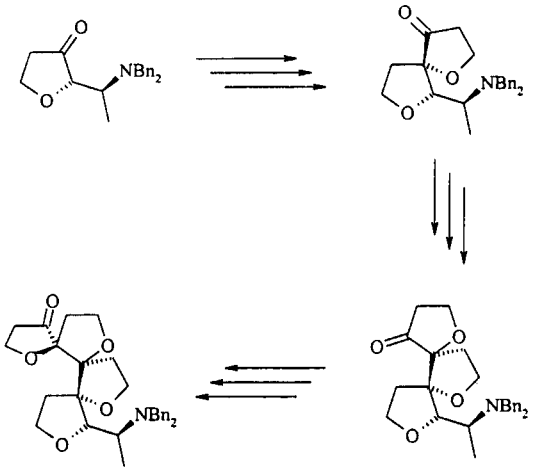


The alanine derived enantiopure furanone reacts with various nucleophiles in a highly diastereoselective fashion affording enantiopure 1,3-amino alcohols arranged at the tetrahydrofuran backbone (Scheme 4) [8]. Following Magnus's idea and applying the repetitive method we were able to prepare the first enantiopure primary helical spiro cycles (Scheme 5) [10,11].

Scheme 4



Scheme 5

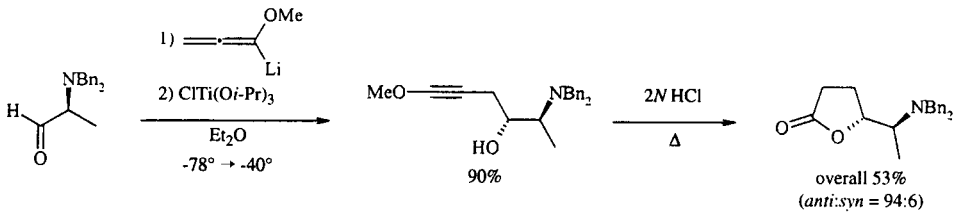


In certain cases the addition to the carbonyl compound could be made more efficient [10] when the lithiated methoxyallene was transmetallated into a cerium(III) species employing cerium trichloride [12]. During these experiments we discovered that transmetallation with chlorotriisopropoxytitanium provided a new species with an inversed regioselectivity. Whereas the lithium compound reacts as nucleophile with the α-carbon (with respect to the methoxy group) the titanium species uses the γ-carbon for C-C bond formation with carbonyl compounds. Thus, the primary adducts with dibenzyl protected amino aldehydes were alkynyl ethers which could be cyclized and hydrolyzed to give enantiopure γ-lactones (Scheme 6) [13,14]. This type of lactones is of interest because they may be converted into HIV-protease inhibitors [15]. In this reaction mode metallated methoxyallene served as a novel homoaldol equivalent.

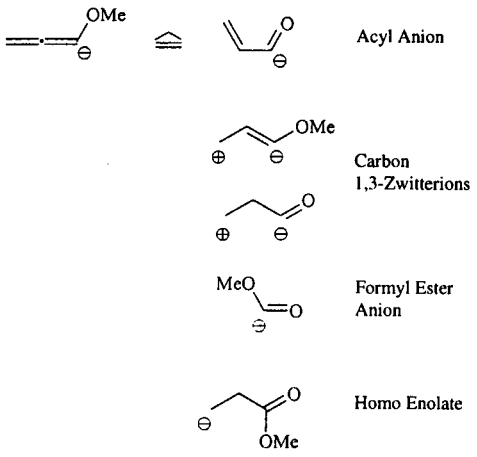
In addition to these transformations we could demonstrate that primary adducts of lithiated methoxyallene with *N*-acylated amino aldehydes could be converted into enantiopure α-hydroxy-β-amino esters by ozonolysis. Depending on the protecting group we were able to either prepare *anti*-configurated compounds [16] or *syn*-compounds, an approach that was used to synthesize the methylester of the taxol side chain in few steps [17]. All these transformations demonstrate that metallated methoxyallene can serve as equivalents for an α,β-unsaturated acyl anion synthon, for carbon 1,3-zwitterionic synthons, for a homo enolate synthon or a formyl ester anion synthon (Scheme 7).

We were surprised that essentially no C-N double bond containing electrophiles had been combined with metallated alkoxyallenes although the potential for syntheses of nitrogen heterocycles should be high. Therefore we started to look at imines and nitrones as electrophiles. Addition of lithiated methoxyallene to *N*-tosyl imines gave the primary adducts in excellent yields (Scheme 8) [18]. Ozonolysis provided α-amino esters whereas cyclization to dihydropyrrole derivatives seems to proceed easier compared with that of carbonyl adducts. This cyclization may be performed under basic conditions, however, it also succeeds employing catalytical amounts of silver

Scheme 6



Scheme 7



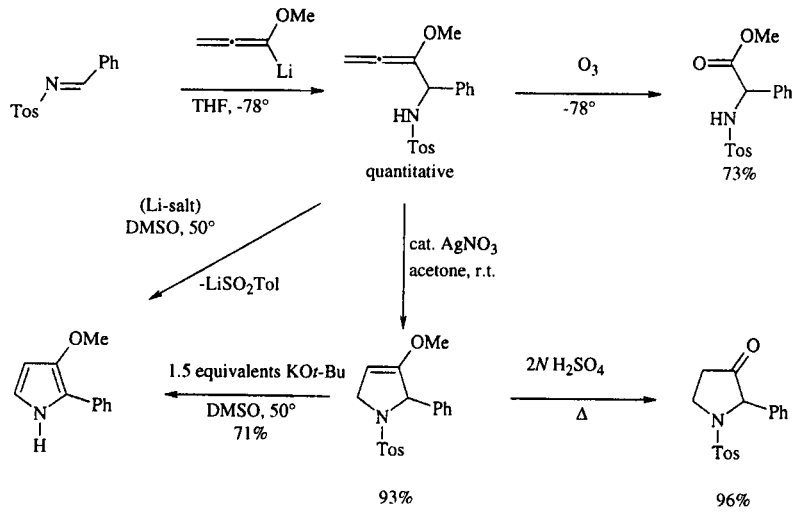
nitrate or palladium catalysts. The *N*-tosylated cyclized compounds could be hydrolyzed to pyrrolidinone derivatives or detosylated to afford 2-substituted 3-methoxypyrroles [19].

Meanwhile, we have obtained many other examples, also with less reactive imines as electrophiles, demonstrating that this type of pyrrole synthesis has no obvious limits. Two charts show syntheses of polycyclic dihydropyrroles (Scheme 9) which might be of interest as redox-active components or as starting materials for stereoselective synthesis of biologically active compounds.

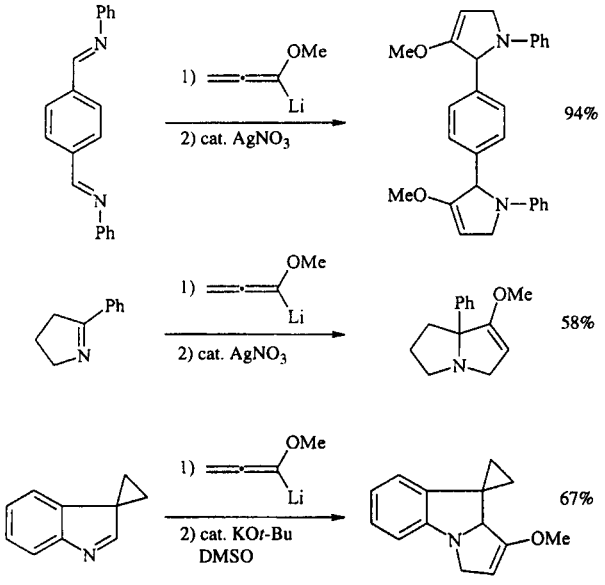
The use of glyceraldehyde derived imines gave primary adducts with the anticipated high *syn*-diastereoselectivity. Cyclization afforded enantiopure dihydropyrrole derivatives (Scheme 10) which are very promising intermediates for synthesis of optically active functionalized pyrrolidinol derivatives. Adducts derived from *N*-alkyl substituted imines have a higher tendency for cyclization. Thus, in several cases we found mixtures of the expected primary product and the dihydropyrrole derivative directly after addition of lithiated methoxyallene to the imine and standard workup [19].

Among electrophiles incorporating a C-N double bond [20] nitrones became very popular during the last few years [21]. We expected hydroxylamine derivatives as

Scheme 8



Scheme 9

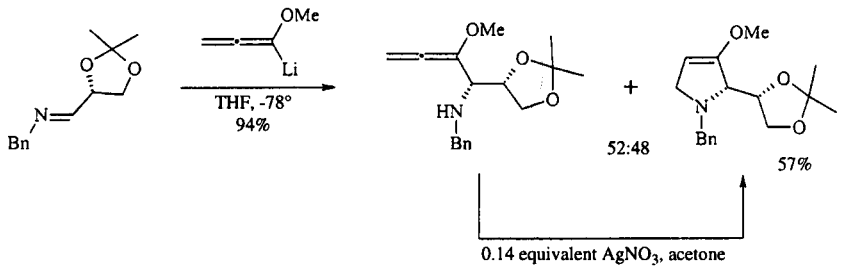


products when lithiated methoxyallene was combined with nitrones. This was the case for a sterically hindered nitrone (Scheme 11) which slowly cyclized to the isomeric 3,6-dihydro-2*H*-1,2-oxazine. However, for all other examples so far investigated we could not detect the primary adduct. Instead, 1,2-oxazines were directly isolated in moderate to excellent yields [22]. The exact mechanism of the cyclization leading to the six-membered heterocycle is not known at the moment [23].

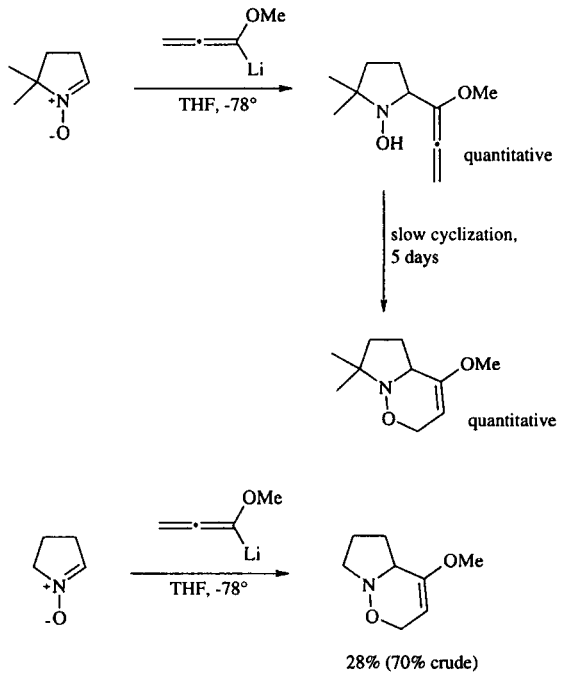
Employing the literature known glyceraldehyde derived nitrone [24] we obtained the *syn*-1,2-oxazine in very good yield and with excellent diastereoselectivity (Scheme 12) [22]. This product was accompanied by a small amount of a 1,3-diene which might formally arise from a retro Diels-Alder reaction of the 1,2-oxazine [25].

Precomplexation of the nitrone with diethylaluminum chloride followed by reaction with lithiated methoxyallene provided the pure *anti*-1,2-oxazine (Scheme 12) [22]. The selective formation of *syn*- or *anti*-1,2-oxazines can be interpreted by the model of Dondoni and Merino developed for additions of simplier organometallic

Scheme 10



Scheme 11

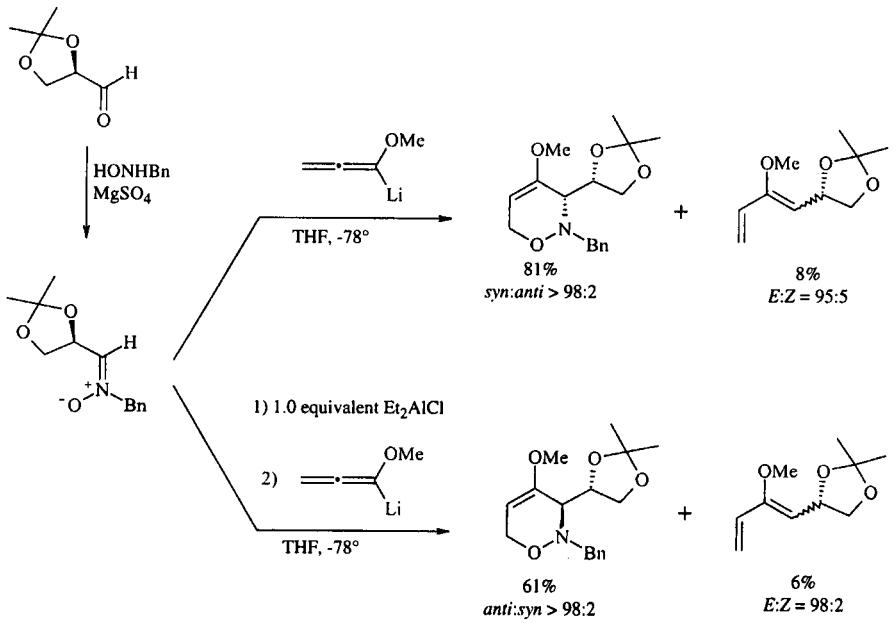


species to nitrones [26]. Addition of lithiated methoxyallene to amino aldehyde derived nitrones proceeded with very good *syn*-selectivity (Scheme 13). However, the complete switch to the *anti*-configuration was so far not possible and probably needs the use of other *N*-protecting groups which prevent competing interaction of the Lewis acid with the amino function [22].

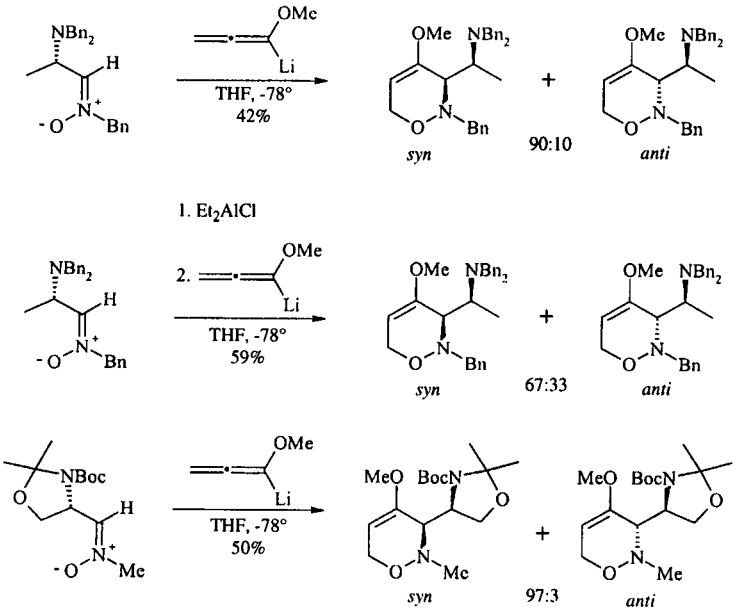
Although the efficiency is not good at the moment, we could extend the method to a simple two-directional synthesis [27] of highly functionalized bis-1,2-oxazines (Scheme 14). Direct addition to an easily available bisnitrone [28] afforded the *syn,syn*-adduct as major component, while precomplexation with diethylaluminum chloride gave predominatingly the *anti,anti*-compounds. Yields are poor since the diastereoselectivity is diminished and more side products (bisdienes and 1,2-oxazinyldienes) are formed, but the bis-1,2-oxazines obtained are of high interest as enantiopure functionalized symmetrical ten-carbon building blocks.

1,2-Oxazines have been very popular intermediates for synthetic adventures in our group for many years [29].

Scheme 12



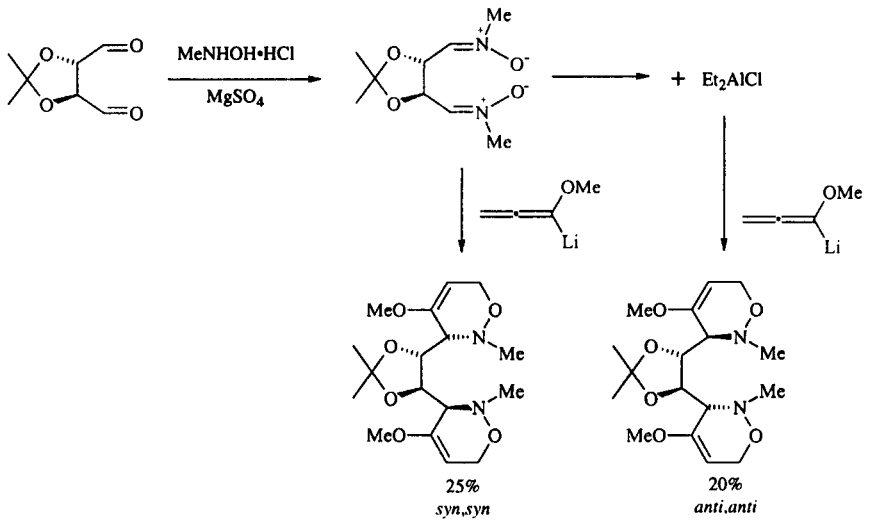
Scheme 13



Therefore, we were glad that we could open a new route to enantiopure, highly functionalized 1,2-oxazines with the [3 + 3] cyclization methodology as described above. The two 1,2-oxazines derived from (*R*)-glyceraldehyde are particularly interesting starting materials for further synthetic manipulations (Scheme 15), and a variety of enantiopure amino alcohols, functionalized amino acids or amino sugar derivatives may possibly be prepared. Therefore, we started to explore stereocontrolled transformations of these 1,2-oxazines.

Hydrogenolyses of *syn*- or *anti*-1,2-oxazines either as a one-step procedure with hydrogen/Pd-C or as a two-step procedure first with hydrogen/Raney-Nickel, followed by application of hydrogen/Pd-C provided 4-aminotetrols with complementary diastereoselectivity (Schemes 16 and 17). From these results we can conclude that with hydro-

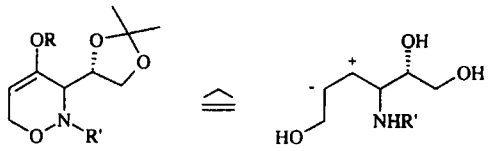
Scheme 14



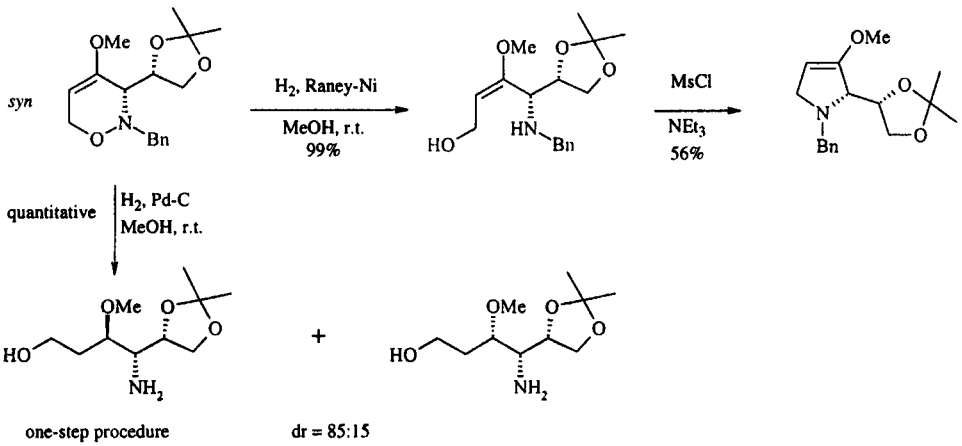
gen/Pd-C the C-C double bond of the 1,2-oxazine is reduced in the very first step [30,31].

The structures of the allyl alcohols could be established by their transformation into dihydropyrrole derivatives and their nmr data. The fully reduced amino alcohols have been cyclized by treatment with mesyl chloride and base stereoselectively affording methoxy pyrrolidine derivatives with defined configuration (Scheme 18) [31].

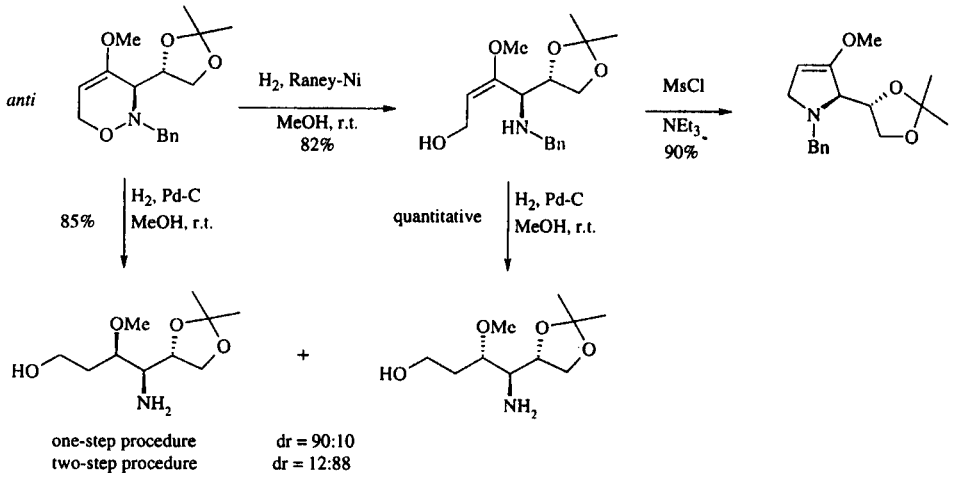
Scheme 15



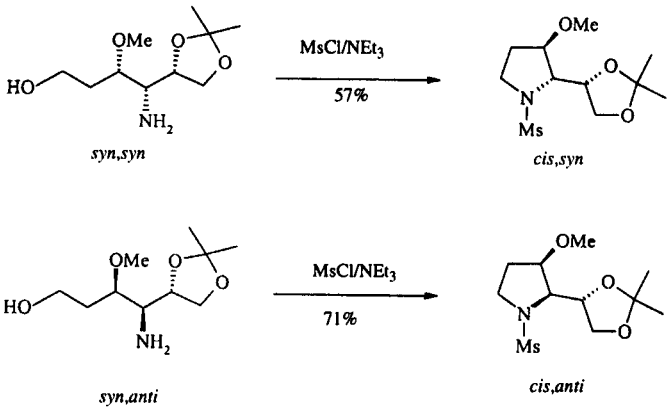
Scheme 16



Scheme 17



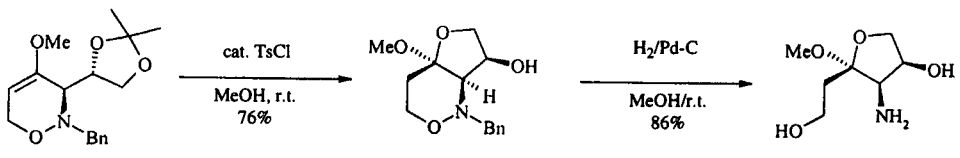
Scheme 18



Solvolysis of the *anti*-adduct led to a bicyclic acetal (Scheme 19) which could be converted into an enantiopure amino furanol derivative in good overall efficiency by hydrogenolysis [30,31]. The corresponding *syn*-adduct should behave similarly.

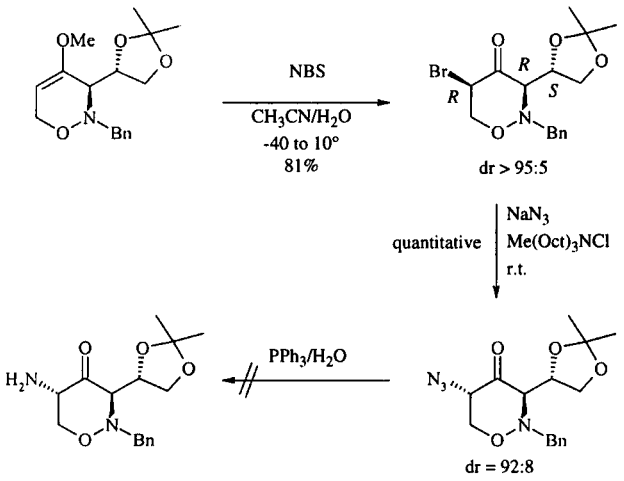
Products with a high potential for further elaboration derive from bromination of *syn*- or *anti*-1,2-oxazine [30,31]. For the bromination product of *anti*-1,2-oxazine we obtained one diastereomer (Scheme 20) whose configuration could unequivocally be determined by an X-ray

Scheme 19



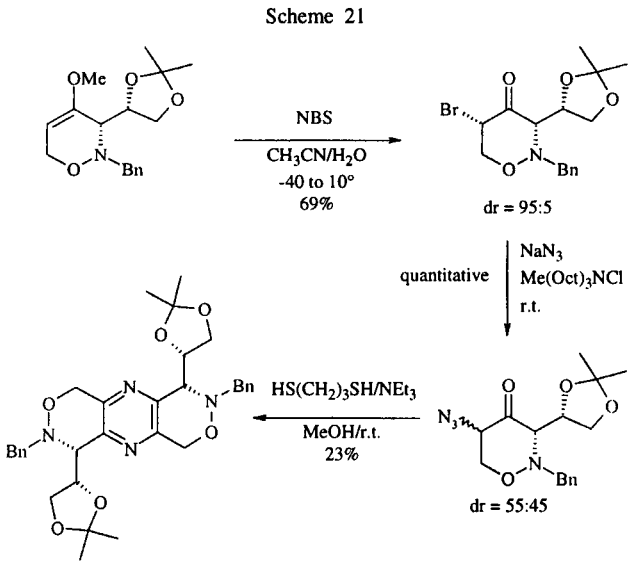
analysis [32]. Quantitative transformation into an azido compound was smoothly achieved, however, the reduction leading to an amino ketone was so far unsuccessful.

Scheme 20



Bromination of *syn*-1,2-oxazine also occurred diastereoselectively, but the azidation proved to be unselective providing a mixture of isomers. Here we received a definite product by attempts to convert the azido ketone into the corresponding amino ketone. However, a dimer was isolated instead, which is probably the selfcondensation product of the anticipated amino ketone followed by dehydration thus providing the pyrazine nucleus [31].

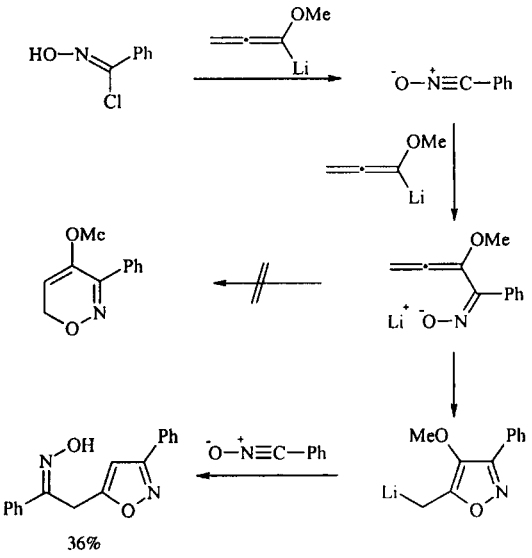
Scheme 21



Many other options are evident with the 1,2-oxazines easily obtained by reaction of lithiated methoxyallene with enantiopure nitrones and we are currently strongly engaged in further exploring this area.

Nitrones are 1,3-dipoles and therefore it was very tempting to expose similar 1,3-dipolar compounds to lithiated methoxyallene. Nitrile oxides are generated by base treatment of hydroximoyl chlorides, and therefore we could hope to trap this 1,3-dipole with lithiated methoxyallene. However, addition of an excess of lithiated methoxyallene to phenylhydroximoyl chloride did not provide the expected 6*H*-1,2-oxazine by a ring closure analogous to that with nitrones, but an isoxazole derivative was isolated in moderate yield (Scheme 22). This compound incorporates two equivalents of the *in situ* generated nitrile oxide and its formation may be plausibly explained by an anionic 1,5-electrocyclization leading to a lithiated methylisoxazole intermediate which reacts with a second equivalent of the nitrile oxide [30].

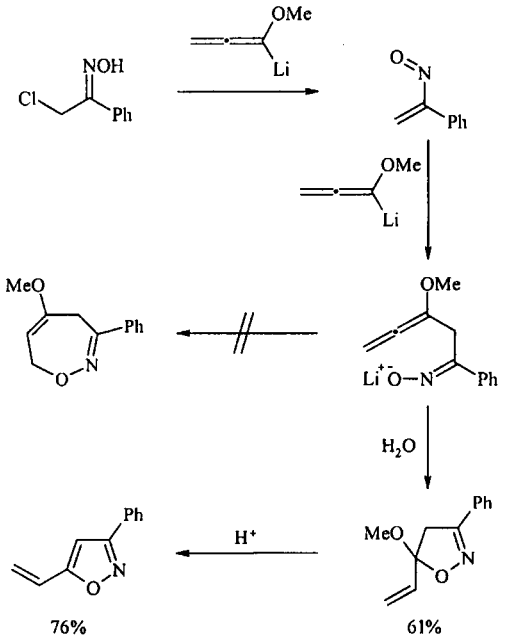
Scheme 22



Nitrosoalkenes may also be suitable electrophiles for lithiated methoxyallene and lead to heterocycles. In one example we received a 1:1 adduct, however, not the desired seven-membered heterocycle was formed, but a 5-vinylisoxazoline (Scheme 23) which after treatment with acid provided a 5-vinylisoxazol [19].

It should be mentioned that Brandsma *et al.* very recently studied the reactions of lithiated methoxyallene with isothiocyanates which gave thiophene or pyrrole derivatives depending on substituents and reaction conditions [33].

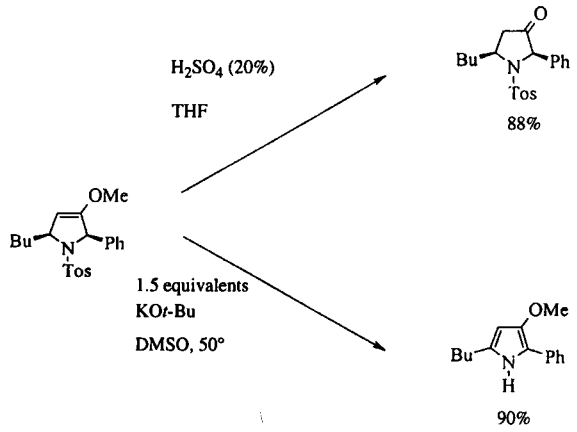
Scheme 23



Recently, we started the investigation of axially chiral 3-substituted 1-alkoxyallenes which should allow syntheses of heterocycles with an additional substituent. Their synthesis is fairly straightforward and lithiation occurs with *n*-butyllithium [19,34]. First experiments revealed that the reaction of the metallated species with imines proceeds, but unfortunately so far with negligible diastereoselectivity (Scheme 24). The cyclization to dihydropyrrole derivatives is possible under conditions developed for the simple methoxyallene adducts. Interestingly, it occurs with high diastereoselectivity and a considerable kinetic preference for the formation of the *cis*-configurated product. Alternatively, the allenyl amine could directly be prepared from the isomeric alkyne and the imine. This route is much shorter and more efficient and should be further explored [19,34].

The *cis*-substituted dihydropyrrole could be hydrolyzed to a pyrrolidinone derivative, or it was aromatized by base treatment affording 4-butyl-3-methoxy-2-phenylpyrrole in excellent yield (Scheme 25) [19,34].

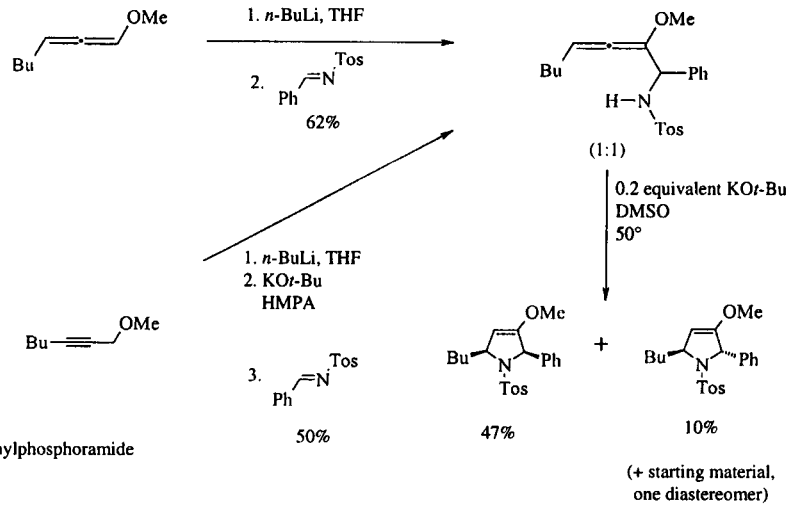
Scheme 25



Conclusion.

Our work, as well as that of other groups, demonstrate that lithiated methoxyallenes are very useful three-carbon building blocks for the construction of functionalized heterocycles. Its reactions with electrophiles provide furan, pyridine, pyrrole and 1,2-oxazine derivatives in a straightforward and highly flexible manner. Of particular interest are chiral systems which allow preparation of a variety of

Scheme 24



HMPA: Hexamethylphosphoramide

enantiopure products. These are important for synthesis of natural products or other biologically active compounds. The reactions of 3-substituted methoxyallenes are almost unexplored but our first experiments reveal that they behave similarly to the parent compound. Therefore a manifold of new highly substituted and functionalized heterocycles will be available by using higher relatives of lithiated methoxyallene.

Acknowledgement.

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