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Asymmetric Synthesis via Nucleophilic Addition to α,β-Epoxyimines

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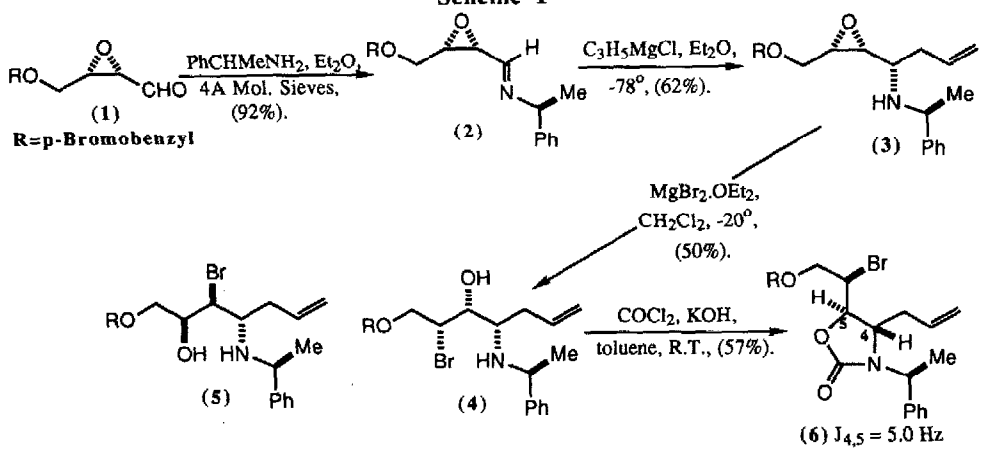
Abstract: *The addition of allylmagnesium chloride to the chiral, non-racemic α,β-epoxyimine (2) is highly diastereoselective, and the facial selectivity can be controlled by the use of $BF_3.OEt_2$; Addition of vinylmagnesium bromide in the presence of this Lewis acid also takes place with high diastereoselectivity.*

α,β-Epoxyaldehydes such as (1) (Scheme 1) are readily available in high optical purity by *via* Sharpless asymmetric epoxidation,[1] and have been shown by ourselves and others to be valuable intermediates for asymmetric synthesis.[2,3] The addition of nucleophiles to the carbonyl group of these systems can be controlled such that either of the two diastereoisomeric products predominates, which can be useful in that it is possible to carry out direct synthesis of materials which are not easily obtained by Sharpless kinetic resolution.[2] In this context it was of interest to explore the use of α,β-epoxyimines of type (2). The products, β,γ-epoxyamine derivatives, are not available by Sharpless epoxidation processes as the corresponding allylic amine derivatives are not substrates for the asymmetric catalyst. This Letter describes our initial work on the addition of simple Grignard reagents to this type of chiral α,β-epoxyimine.[4]

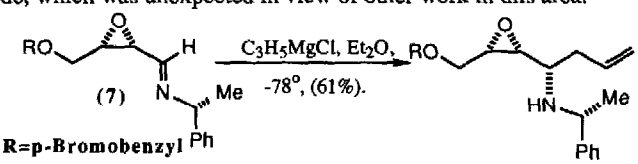
Immediate synthetic targets include amino-sugars, oxygenated amino acids, and analogues thereof. In view of this the work concentrated on the addition of allyl and vinylmagnesium halides to the *cis*-α,β-epoxyimine (2), since the *cis*- stereochemistry provided the best chance for high diastereoselectivity,[5] and manipulation of the double bond could give access to the desired types of targets. This α,β-epoxyimine was prepared from the corresponding aldehyde which itself is readily available in essentially 100% optical purity,[6] and S-α-methylbenzylamine was chosen as it had been shown that good diastereoselectivity could be obtained in the addition of allylic nucleophiles to imines derived from this amine and its antipode.[7]

Reaction of the α,β-epoxyimine (2) with allylmagnesium chloride gave one major product after chromatography, which was clearly either the β,γ-epoxyamine (3) or the product with the opposite stereochemistry at the new chiral centre. That it corresponded to (3) was demonstrated by reaction with magnesium bromide etherate to give a mixture of (4) and (5), and conversion of the *vic*-aminoalcohol (4) to the oxazolidinone (6). Analysis of the 300 MHz ^{1}H n.m.r. spectrum revealed the coupling constant between H-4 and H-5 to be 5.0 Hz, typical of a *trans*-isomer,[8] which would correspond to a 'chelation controlled' addition of the Grignard reagent to the imine (*vide infra*).[9]

Scheme 1

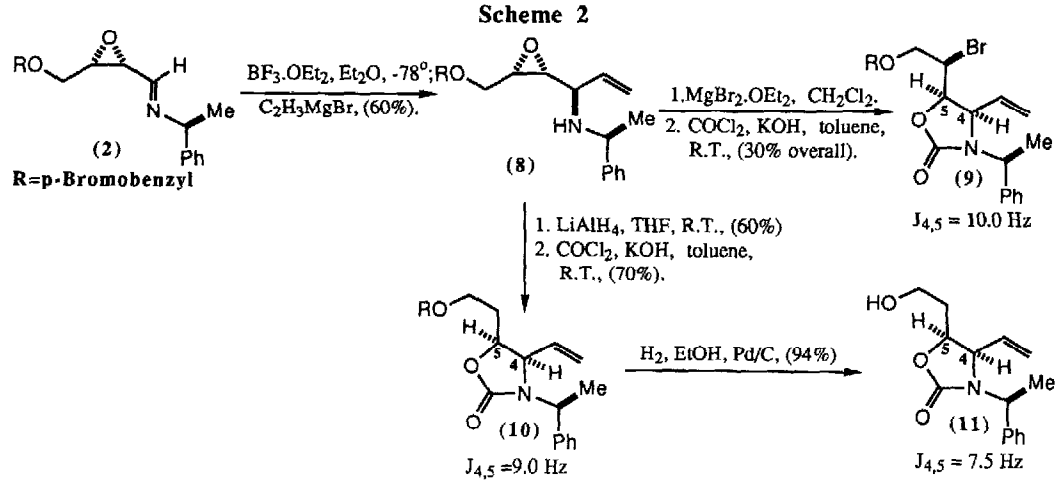


The diastereoisomeric α,β-epoxyimine (7) derived from aldehyde (1) and R-α-methylbenzylamine was prepared and reacted with allylmagnesium chloride again with chelation control. The stereochemistry of the group on nitrogen appears to have little influence on the stereochemical outcome of the reaction of allylmagnesium chloride, which was unexpected in view of other work in this area.[7]



The products from these experiments with allylmagnesium chloride could in principle be used as precursors to either 2,3-dideoxy-3-amino sugars,[10] or to polyoxygenated β-aminoacids[11] (*inter alia*). In order to widen the potential of this methodology further the addition of vinylmagnesium bromide was investigated, since this could provide access to polyoxygenated α-amino acids and other related systems.

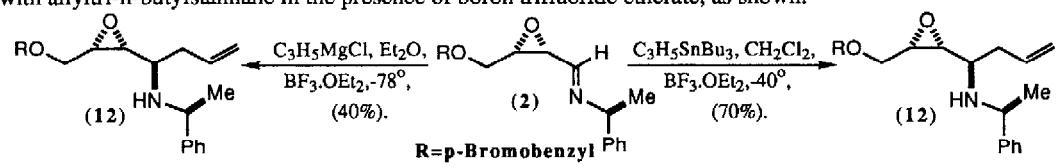
Scheme 2



Attempts to react the α,β-epoxyimine with vinylmagnesium bromide alone were unsuccessful, whereas if the imine was treated with $BF_3.OEt_2$ prior to addition of the Grignard reagent, a good yield of a diastereoisomerically pure addition product (8) was obtained after chromatography (Scheme 2).

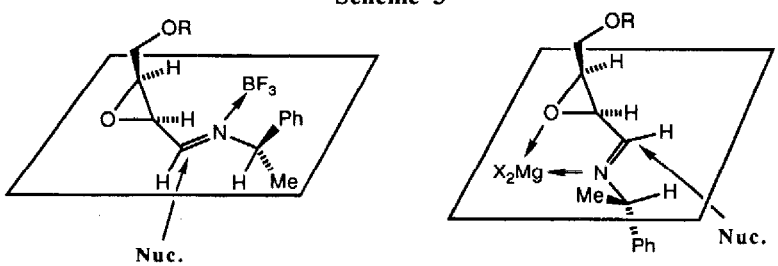
As earlier, addition product (8) was treated with magnesium bromide etherate followed by phosgene. Isolation of the oxazolidinone (9) and analysis of the ^1H nmr spectrum showed $J_{4,5}$ to be 10.0 Hz, suggesting it to be a *cis*- isomer. However, a recent report suggests that such stereochemical correlations must be treated with caution when one of the substituents on the oxazolidinone is vinylic.[12] In order to provide a simpler system, (8) was treated with lithium aluminium hydride followed by phosgene, to provide the oxazolidinone (10), and again $J_{4,5}$ suggested a *cis*- isomer (9.0 Hz). To remove doubts due to the presence of the vinylic group, oxazolidinone (10) was subjected to catalytic hydrogenation and again, analysis of the ^1H nmr spectrum of (11) revealed a relatively large value (7.5 Hz) for $J_{4,5}$ indicative of a *cis*- isomer (Scheme 2).

It is interesting to note that the addition of vinylmagnesium chloride in the presence of boron trifluoride etherate gives the 'non-chelation control' product, opposite to that observed with allylmagnesium chloride in the absence of this Lewis acid. In order to clarify the role of the Lewis acid in these additions, allylmagnesium chloride was added to a solution of epoxyimine (2) pre-treated with boron trifluoride etherate. None of the previously observed 'chelation controlled' product was detectable in the ^1H nmr spectrum of the crude product. Chromatography gave a two-component mixture, the major component corresponding to the 'non-chelation controlled' addition product (12). This same product was obtained much more cleanly on treatment with allyltri-n-butylstannane in the presence of boron trifluoride etherate, as shown.



It would appear that the presence of boron trifluoride etherate alters the course of the addition of both the Grignard reagents investigated here. One rationalisation offered in Scheme 3 is that in the presence of boron trifluoride, a complex analagous to (13) is formed, which blocks chelation with magnesium ions. In the absence of boron trifluoride etherate, it is possible that a Lewis acidic magnesium species provides a chelated complex (14). Addition from the less hindered face then gives rise to the observed products.

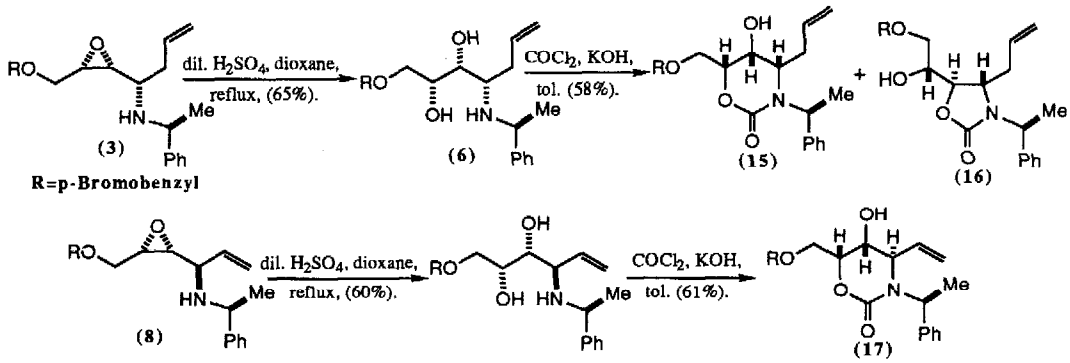
Scheme 3



In most cases, any synthetic application of this methodology will involve the opening of the epoxide ring at some stage. It was therefore of some interest to investigate this process. Opening of these addition products with magnesium bromide etherate was not selective, but the opening of (3) and (8) with aqueous acid appeared to be highly regioselective producing in both cases a single diol. In both cases the crude product was treated with phosgene under basic conditions to provide compounds for characterisation (Scheme 4). It is interesting that diol (6) produces a mixture of oxazinone (15) and oxazolidine (16) (1.3:1), whereas the diol from (8) cyclises to give only the oxazinone (17). The selectivity of this latter process is understandable in terms of the relative stereochemistry at C-3 and C-4, as formation of the corresponding oxazolidinone would

produce a *cis*- isomer, and presumably transition states which would lead to this isomer would suffer destabilisation due to increasing steric repulsion as the two large groups approached this *cis*- relationship. The only other opening to be investigated so far is the reduction of (8) with lithium aluminium hydride which appeared to be completely selective (Scheme 2).

Scheme 4



In conclusion we have shown that α,β-epoxyimines can be used for the C-C constructive stereocontrolled synthesis of some β,γ-epoxyamines, which themselves undergo selective transformations of synthetic potential.

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