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[2,3]-Meisenheimer rearrangement of *N*-allyl phenylglycinol derivatives. N–C versus C–C chirality transfer

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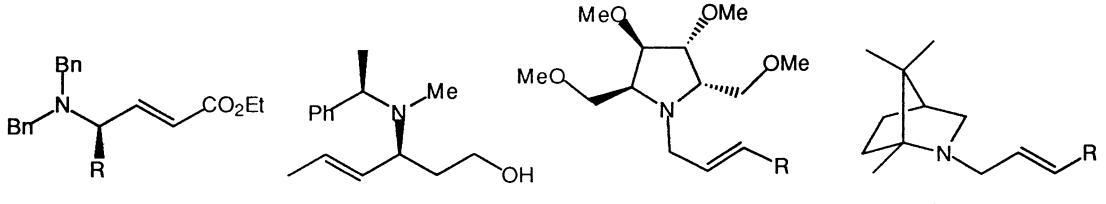
Abstract

The [2,3]-Meisenheimer rearrangement has been investigated on various allylic amines bearing phenylglycinol as a chiral appendage. The relative importance of N–C and C–C chirality transfer is discussed.

The Meisenheimer rearrangement, first reported in 1919, is one of the less studied [2,3]-sigmatropic rearrangements.[1] In particular, only a few examples illustrate its potential for asymmetric synthesis. Three kinds of chirality transfer can be considered in the course of this rearrangement (Fig. 1).



1 **2** **3** **4**

Figure 1.

The first one consists in a 1,3-'self-immolative' asymmetric transformation, which was reported to proceed efficiently by Reetz[2] for **1** and more recently by Davies for compound **2**.[3] Enders and Kempen reported a second approach for **3**, based on the use of a C_2-symmetric auxiliary, which avoids the problem of the selective oxidation of the nitrogen; however only a moderate asymmetric induction was observed.[4] Since tertiary amine *N*-oxides are configurationally stable species, it is also possible to have chirality transfer from the nitrogen to the

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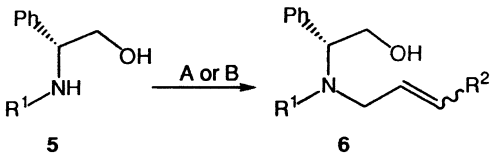
carbon center. Although this chirality transfer has been suggested to proceed in an efficient manner by the pioneering work of Inouye and co-workers, asymmetric oxidation of tertiary amines usually gives amine oxides with low enantioselectivity.[5]

The stereospecific obtention of chiral *N*-oxides can be achieved using a chiral auxiliary on the substrate. This strategy was mainly used by Coldham's group, who extensively investigated the [2,3]-Meisenheimer rearrangement starting from chiral non-racemic tertiary allylic amines **4**.[6] Despite recent successful results, the separate contribution of each chiral element in the final d.e. observed remained unclear, since *N*-oxide could not be isolated prior to rearrangement.

We recently reported an easy access towards enantiopure α-substituted propargylamines using (*R*)-phenylglycinol as a chiral auxiliary.[7] Since this methodology allows the preparation of analogous allylic amines, we decided to study the relative efficiency of the three possible chirality transfers occurring in the Meisenheimer rearrangement starting from such derivatives.

α-Unsubstituted allylic amines **6a–f** were prepared according to two classical ways, starting from *N*-protected phenylglycinol (Scheme 1).



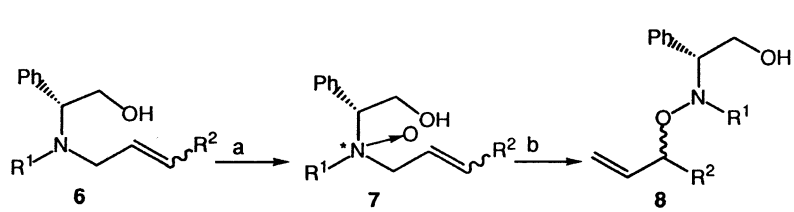
5 **6**

compound	method	configuration	R^1	R^2	Yield %
6a	A	*E*	Me	Ph	71
6b	A	*E*	Bn	Ph	92
6c	A	*E*	Me	COOMe	74
6d	A	*E*	Bn	COOMe	62
6e	B	*Z*	Me	*n*-Pent	58
6f	B	*E*	Me	*n*-Pent	55

Scheme 1. *Reagents and conditions* : Method A : $BrCH_2CH{=}CHR^2$, MeCN, Na_2CO_3, Δ. Method B : (a) $R^2{-}C{\equiv}CH$, aq. HCHO, CuCl cat., $ZnBr_2$, H_2O/dioxane, 70°C. (b) DIBAH, toluene or H_2, $Pd/BaSO_4$, quinolein, MeOH

The Cu-mediated Mannich alkynylation was performed in water, and required one equivalent of $ZnBr_2$ for activation of the transient oxazolidine. *Z* configuration of the double bond was controlled by the reduction step.

N-oxidation was then performed using a standard procedure (Scheme 2). The *N*-oxides **7a–f** were stable enough after being isolated, and the d.e. of the oxidation step could be determined by ^1H NMR analysis. Best results were obtained when performing the oxidation at low temperature (–78°C). The absolute configuration of the newly created asymmetric center was not determined at this step.



6 **7** **8**

compound	d.e %	compound	d.e %
7a	74	**8a**	0
7b	51	**8b**	0
7c	72	**8c**	0
7d	54	**8d**	0
7e	55	**8e**	0
7f	58	**8f**	0

Scheme 2. *Reagents and conditions*: (a) *m*CPBA, Na_2CO_3, CH_2Cl_2, –78°C, 1 h. (b) Acetone, rt, 5 h

The *N*-oxides **7a–f** proved to be highly stable in dichloromethane or chloroform, probably due to the presence of an intramolecular hydrogen bonding with the pendant hydroxyl group.[8] Lowering the polarity of the solvent led to an increase of the rearrangement rate. In acetone, compounds **8a–f** were obtained in quantitative yield after less than 5 hours at room temperature. However, in each case, no diastereoselectivity was observed after the rearrangement. Lowering the reaction temperature (–20°C) led to a large decrease of chemical yield, without any selectivity improvement. *Z* allylic *N*-oxide **7e** rearranged about five times slower than its *E* isomer **7f**.

Such a poor chirality transfer has already been described by Coldham on allylic amines derived from prolinol.[9] This loss of selectivity was explained by the reversibility of the Meisenheimer rearrangement, which could lead to some racemization of the final hydroxylamine.

Another explanation can be proposed for this phenomenon (Fig. 2). Two reactive conformers leading to opposite diastereoselectivities can exist in the reaction mixture. They are in equilibrium by a simple N–C_1 and C_1–C_2 rotation.[10] Obtention of a good chirality transfer requires therefore that this equilibrium be strongly shifted towards one conformer, regardless of the *N*-oxide stereochemistry.

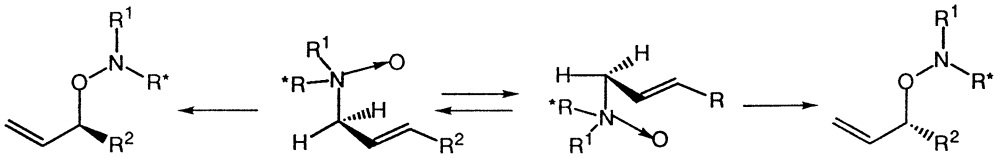
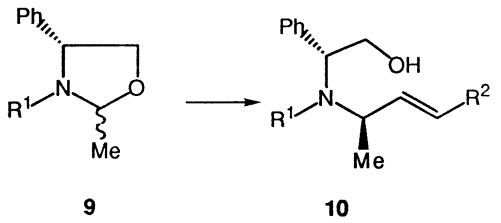


Figure 2.

This shift can be obtained by tuning interactions between the chiral auxiliary and the allylic moiety, or by introducing a substituent α to the nitrogen. We therefore investigated the rearrangement of α-substituted allylic amines **10 a–b** (Scheme 3).



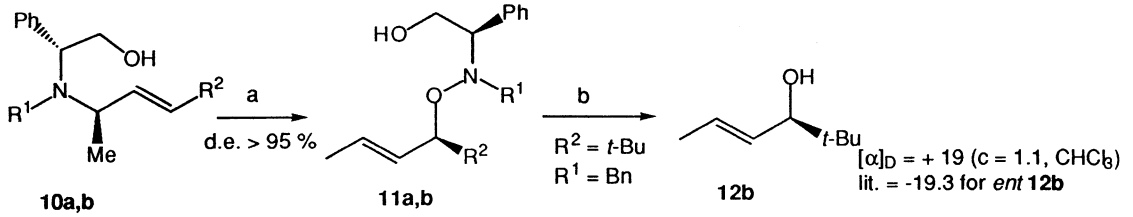
9 **10**

	R^1	R^2	Yield %	d.e. %
10 a	Bn	*t*-Bu	91	97
10 b	Me	*n*-Pent	51	96

Scheme 3. *Reagents and conditions*: R^2–C≡CH, DIBAL, toluene, 4 h, then **9**, 0°C, 1 h

These compounds were obtained in a straightforward manner by addition of mixed alkenylaluminum compounds on oxazolidines **9a–b**. This reaction proved to be as diastereoselective as already reported for the addition of alkynylaluminum reagents.[7] Absolute configuration of the newly created asymmetric center was established by chemical correlation with the corresponding propargylic compounds.[7]

Under standard oxidation conditions, these compounds led very rapidly to hydroxylamines **11a**–**b**, in a quantitative yield and with complete chirality transfer (Scheme 4). Absolute configuration of compounds **11** was determined by chemical correlation of **11b** with **12b**[11], and the good agreement of the specific rotation with the value reported in the literature indicates that reductive cleavage occurred without racemization, as already described by Davies and co-workers.[3] The introduction of a substituent α to the nitrogen led to a dramatic increase of rearrangement rate.



Scheme 4. *Reagents and conditions*: (a) i. *m*CPBA, Na_2CO_3, CH_2Cl_2, 0°C, 1 h. ii. Acetone, rt, 1 h, quantitative. (b) Na, NH_3, 84% from **10b**

Although *N*-oxides could not be isolated for such derivatives, it is highly probable that, as in the case of compounds **7a**–**f**, their formation was not fully stereoselective at 0°C. *N*-oxide configuration is in this case unimportant, and the excellent C–C chirality transfer observed is only due to the new asymmetric center, which controls the conformation of the reactive species, as already reported by Reetz and co-workers.[2]

In conclusion, this study shows that the *N*-oxide configuration does not play an important role in the [2,3]-Meisenheimer rearrangement if the conformation of allylic amine is not carefully controlled. This can be done by using cyclic rigid chiral auxiliary,[4,6] or by the introduction of a substituent α to the nitrogen. In this case, diastereoselective *N*-oxide formation is unimportant, since the C–C chirality transfer is highly efficient. In addition, we have shown that the use of mixed organoaluminum reagents chemistry enables the straightforward preparation of diastereomerically pure α-substituted allylic amines from readily available oxazolidines. This methodology, followed by a very efficient [2,3-] Meisenheimer rearrangement, provides a simple and scalable access towards various enantiopure allylic alcohols.

Acknowledgements

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