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Excellent diastereoselective allylation of camphor derived glyoxylic oxime ethers mediated by a Lewis acid

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Abstract—The nucleophilic allylation of camphor derived glyoxylic oxime ethers was carried out using allyltributyltin in the presence of $Sn(OTf)_2$ affording the corresponding homoallylic amines in high chemical yields (up to 94%) and excellent stereoselectivities (up to >99%).

The allylation of a carbonyl group constitutes one of the most important carbon–carbon bond forming reactions and has received considerable attention in recent years.[1] Allylation of C=N bond derivatives provide homoallylic amines which serve as structural subunits and important building blocks in the synthesis of nitrogen containing natural products.[2] The stereoselective nucleophilic allylation of imines,[3] hydrazones[4] to give homoallylic amines is well documented in the literature. However, unsatisfactory results are obtained in some cases of the nucleophilic allylation of C=N bonds due to the low electrophilicity of imines and imine derivatives. On the other hand, the allylation of glyoxylic oxime ethers, to provide the corresponding allylglycine has not widely studied.[5] The palladium–indium iodide-mediated allylation of camphorsultam derived glyoxylic oxime ether in aqueous media has been reported. The development of alternative methods for the asymmetric synthesis of the α-amino acid functional array is of considerable importance. The poor electrophilicity of the C=N bond in glyoxylic oxime ether can be enhanced by coordination with a Lewis acid. Here, we wish to report on the diastereoselective nucleophilic allylation of camphor derived glyoxylic oxime ethers that provide a route to the preparation of homoallylic α-amino acids. Various camphor derived chiral auxiliaries have been synthesized in this laboratory and have proved to be useful stereocontrollers in asymmetric synthesis.[6] Excellent material yields and stereoselectivity are obtained for these reactions. The stereochemical course of the reactions is proposed.

The camphor derived *N*-phenyl[6d] and *N*-tosyl camphorpyrazolidinones[7] (**B** and **C**) were prepared in this laboratory recently. Our initial studies focused on the nucleophilic allylation of camphorsultam derived glyoxylic oxime ether. Various allylmetal reagents, Lewis acids and solvents were examined and most of the reactions led to either no reaction or poor stereoselectivity (data not shown). A satisfactory result was obtained when the reaction was carried out using allyltributyltin (2.0 equiv) in CH_3CN at rt in the presence of $Sn(OTf)_2$ for 0.5 h (Table 1, entry 1). The stereoselectivity was improved when the reaction was carried out at a lower temperature and further optimized to 91% de when the reaction was carried out at −40 °C (entries 2–4). Since oxime ethers are known to be excellent electron acceptors in radical reactions, the above reaction using the allyltributyltin reagent may proceed via a radical pathway. To examine this possibility, a similar reaction was carried out in the presence of a radical scavenger 1,4-cyclohexadiene. The allylation product was obtained in 88% yield and 89% de indicating that an allyl radical species was not generated and that the reaction proceeds via an ionic mechanism.[8] The diastereoselectivity was determined by ^1H NMR and HPLC studies of relevant peaks. The absolute stereochemistry of the newly generated stereogenic center in the major diastereomer **2** (Xc = **A**) was assigned as an *S* configuration, deduced from the single crystal X-ray analysis.

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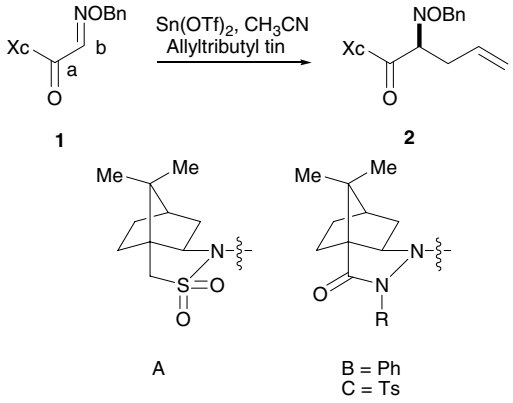
Table 1. Diastereoselective allylation of glyoxylic oxime ethers using allyltributyltin in the presence of $Sn(OTf)_2$[a]



Entry	Xc	*T* (°C)	*t* (h)	Yield[b] (%)	de[c] (%)	Abs. conf.
1	**A**	rt	0.5	92	56	*S*
2	**A**	0	1	90	74	*S*
3	**A**	−25	1	91	78	*S*
4	**A**	−40	1	90	91	*S*[d]
5[e]	A	−40	1	88	89	*S*[d]
6	**B**	−40	1	92	>99	*S*[d]
7[f]	**C**	−40	1	94	>99	*S*[g]

[a] Unless otherwise specified, all reactions were carried out in CH_3CN at the temperature indicated using **1** (0.13 mmol), allyltributyltin (2.0 equiv) and $Sn(OTf)_2$ (1 equiv).
[b] Isolated yield.
[c] Ratios of diastereomers were determined by ^1H NMR analysis of relevant peaks and HPLC analyses of crude products.
[d] The absolute stereochemistry of the newly generated stereogenic center was deduced by single crystal X-ray analysis.
[e] In the presence of 1,4-cyclohexadiene.
[f] 10 equiv of allyltributyltin was used.
[g] Absolute stereochemistry is assigned by analogy.

To examine the scope and applicability of this method, various oxime ethers bearing a chiral auxiliary were studied. Camphor derived glyoxylic oxime ethers **B** and **C** were subjected to the optimized reaction conditions. Allylation of *N*-phenyl and *N*-tosyl camphorpyrazolidinones derived oxime ethers afforded homoallylic amines in excellent yields and diastereomeric excess (entries 6 and 7). The allylation of oxime ethers derived from other auxiliaries ((−)-4-phenyl-oxazolidin-2-one) and some ester linked chiral auxiliaries (10,10-diphenyl-2,10-camphordiol,[6e] (+)-menthol and (−)-*N*-methylephedrine) led to poor stereoselectivities.

A single crystal X-ray analysis of **1** (Xc = **A**) indicates that N–(CO) is oriented *anti* to the sulfonyl group to minimize dipole–dipole interactions and the carbonyl and imino groups exist in a *s-cis* conformation. On the other hand, for *N*-phenyl camphorpyrazolidinones (Xc = **B**), the carbonyl and imino functionalities are arranged in a *s-trans* conformation with the amide carbonyl group oriented toward the phenyl group as indicated by single crystal X-ray analysis. By analogy to the *N*-phenyl camphorpyrazolidinone derived α-keto amides,[6b] the carbonyl and imino groups are oriented in a *s-trans* arrangement in **1** (Xc = **C**) with the amide group facing away from the tosyl functionality. The exact mechanistic explanation for the reaction remains unclear at this moment. To rationalize the stereoinduction bias of the reaction, a series of ^{13}C NMR and FTIR spectra were obtained. A comparison of the ^{13}C NMR spectrum of the pure substrate with that of a mixture of equal amounts of α-imino amides **1** and $Sn(OTf)_2$ was obtained. The chemical shift in carbons a and b of the pure substrate and the chemical shift difference (shown in parenthesis after complexation with $Sn(OTf)_2$) are tabulated in Table 2. The ^{13}C NMR spectral analysis indicates that $Sn(OTf)_2$ chelates strongly with oxime nitrogen and adjacent carbonyl when auxiliary **B** is used.

Further, significant S=O group stretching bands difference were observed when α-imino amide **1** (Xc = **A** and **C**) was complexed with $Sn(OTf)_2$ by FTIR spectroscopy. The IR stretching band corresponding to an S=O group of 1260.5 and 1175.1 cm^{-1} were observed for auxiliaried **A** and **C** derived substrates. A new stretching band at 1245.9 and 1164.5 cm^{-1} was developed for each complex, respectively. Based on these findings, the high degree of stereoselectivity can be rationalized by the chelation of the Lewis acid with **1** as shown in Figure 1. For the two sulfonyl functionalities containing auxiliaries

Table 2. The ^{13}C NMR chemical shift comparison of pure substrates **1** and after complexation with $Sn(OTf)_2$

Entry	**1** (Xc =)	Carbon a (Δδ)	Carbon b (Δδ)
1	**A**	160.37 (+1.04)	143.25 (−0.54)
2	**B**	158.91 (−2.84)	144.23 (−2.24)
3	**C**	161.78 (+0.10)	143.71 (−0.51)

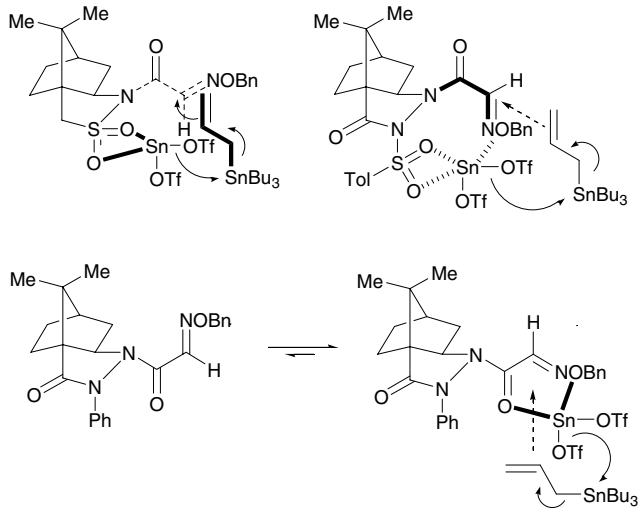


Figure 1. Proposed mechanism of the asymmetric allylatin.

(Xc = **A** and **C**), the Sn atom coordinates with the two sulfonyl oxygen atoms. On the other hand, for **1** (Xc = **B**), the Lewis acid coordinates to the carbonyl and α-oxime ether groups to form a transition state species with a five-membered ring. The allyl group then attacks from the *si* face to afford the desired product.

In summary, three camphor derived glyoxylic oxime ethers were prepared and subjected to the allylation condition using allyltributyltin to give the homoallylic amines in high chemical yields and excellent stereoselectivities in the presence of $Sn(OTf)_2$. Further synthetic applications of camphor derived glyoxylic oxime ethers are under progress.

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