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Enantioselective Allylation of α-Ketoester Oximes with An External Chiral Ligand: Asymmetric Synthesis of Allylglycines and Allylalanine

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Abstract: A highly enantioselective allylation of oximes of α-ketoesters is described with phenyl substituted chiral bis(oxazoline) as external ligand of allylzinc reagents. This method provides an efficient and convenient access to N-benzyloxy allylglycine, allylglycine and chain substituted variants with high enantiomeric purities. Copyright © 1996 Elsevier Science Ltd

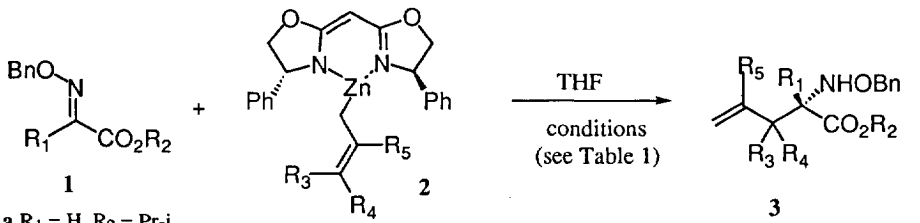
Asymmetric allylation of imines is a well-established method for the synthesis of enantiomerically pure or enriched homoallylic amines.[1,2] However, the enantioselective synthesis of homoallylic amines using external chiral reagents or catalysts is still relatively unexplored. To date, only one example has been reported by Itsuno and co-workers,[3] who achieved moderate enantioselectivities in the reaction of imines with chiral allylborane reagents.

Enantiomerically pure or highly enriched allylglycine and its analogs are very useful chirons for the synthesis of pharmacologically important molecules,[4] as well as of natural products.[5] Although a number of syntheses of optically active allylglycines are known,[6] the majority of these employ methods that utilize chiral auxiliaries associated with the substrate itself. Such auxiliaries have to be installed before and removed after reactions, thus adding to the overall number of steps. For example, a recent synthesis of D- and L-allylglycine involves the preparation of cyclic diastereomeric nitrones from L-menthone, and reacting them individually with allylsilanes in an overall five-step process.[6a] We recently reported a convenient method for the synthesis of enantiomerically enriched allylglycine and its analogs (62-99%ee) using Zn-mediated allylation of glyoxylic acid oxime derivatives in aqueous solution with camphorsultam as a chiral auxiliary.[7] In this paper, we report an enantioselective allylation of α-ketoester O-benzyl oximes with the aid of an external chiral bis(oxazoline) ligand.[8] This constitutes a one-step synthesis of immediate precursors to D- or L-allylglycines and their chain-substituted variants from readily available compounds.

The general reaction for the enantioselective allylation of the α-ketoester oximes is shown in Scheme 1. Initially, the phenyl substituted bis(oxazoline) allylzinc reagent **2a**, prepared by Nakamura's method,[9] was reacted with oxime **1a** in THF at -78 °C, and the corresponding N-benzyloxy allylglycine derivative was obtained in 87% yield with only 67% ee. Simply changing the *iso*-propyl ester **1a** to the *tert*-butyl ester **1b** resulted in a substantial increase of enantioselectivity to 93% (Table 1, entry 1).[10] When the reaction was done

at 0 °C, the ee decreased dramatically to 57%. Other chiral bis(oxazoline) ligands with benzyl, and even bulkier *tert*-butyl groups instead of the phenyl group gave essentially no enantioselectivity. Next, we extended this reaction to other allylzinc reagents derived from readily available commercial compounds (Scheme 1, Table 1). In contrast to the reactions with the sultam auxiliary[7] where 2-substituted allyl bromides gave moderate diastereoselectivities, good to excellent selectivities were secured employing the phenyl substituted bis(oxazoline) ligand of type **2**. For example, methallyl and 2-phenyl substituted allylzinc reagents **2b** and **2c**

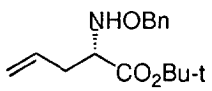
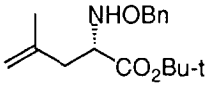
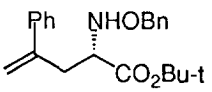
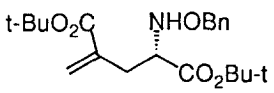
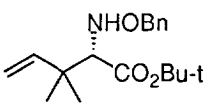
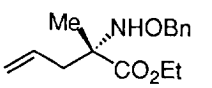
Scheme 1



a R_1 = H, R_2 = Pr-i
b R_1 = H, R_2 = Bu-t
c R_1 = Me, R_2 = Et

a R_3 = R_4 = R_5 = H
b R_3 = R_4 = H, R_5 = Me
c R_3 = R_4 = H, R_5 = Ph
d R_3 = R_4 = H, R_5 = CO_2Bu-t
e R_3 = R_4 = Me, R_5 = H

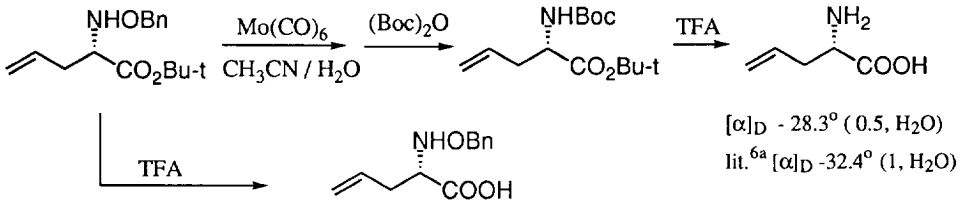
Table 1: Asymmetric synthesis of N-benzyloxy L-allylglycine and analogs

Entry	oxime	allylzinc	product		temp.	time	yield[a]	e.e.[b]	abs.config.
1	**1b**	**2a**		**3a**	-78°C	1h	82%	93%	*S*[d]
2	**1b**	**2b**		**3a**	-78°C	1h	74%	92%	*S*[d]
3	**1b**	**2c**		**3c**	-78°C	1h	90%	87%	*(S)*[e]
4	**1b**	**2d**		**3d**	-78°C	0.5h	89%	74%[c]	*S*[d]
5	**1b**	**2e**		**3e**	-78°C	1h	62%	94%	*(S)*[e]
6	**1c**	**2a**		**3f**	-23°C	7h	72%	91%	*(S)*[e]

a. Isolated yield. b. Ee's were determined by forming Mosher's amides except otherwise noted. c. See text and Scheme 3. d. Assigned by direct comparison with reported data. e. Assigned by analogy.

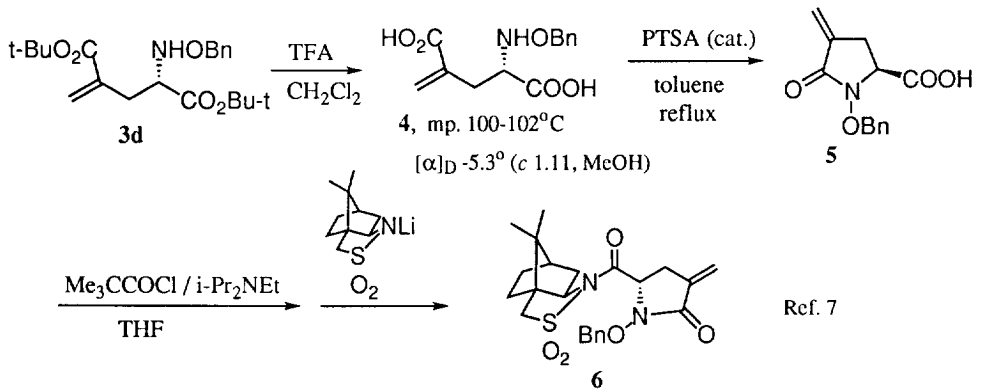
gave products having 92% and 87% ee respectively (Table 1, entries 2 and 3), while *tert*-butyl ester substituted allylzinc reagent **2d** gave product **3d**, with slightly decreased selectivity (entry 4). The prenylzinc reagent **2e** gave the γ-addition product with 94%ee (entry 5). Finally, reaction of allylzinc reagent **2a** with oxime **1c**, derived from pyruvic acid, led to the corresponding α-methyl substituted L-allylglycine derivative **3f** with high enantioselectivity (entry 6).[11] It is of interest to note that the chiral bis(oxazoline) ligand could be easily separated from the products, and recovered without losing its optical activity.[9] The allylation products could be easily transformed into the corresponding synthetically useful L-allylglycine and its substituted derivatives by simple functional manipulations as shown in Scheme 2. Of particular interest is the selective cleavage[12] of the O-benzyl group without affecting the double bond.

Scheme 2



The enantiomeric purities of the allylation products were determined by NMR analysis of the Mosher's amides of the corresponding hydrogenolyzed amino acids (**3a**, **3b**, **3e**, **3f**), or the amines resulting from selective cleavage of the O-benzyl group (**3c**). The stereochemistry of **3a** and **3b** was determined by comparing the optical rotation values of the corresponding N-benzyloxy L-allylglycines, L-allylglycines or the saturated L-α-amino acids. In the case of **3d**, it was transformed into the corresponding known[7] camphorsultam derivative **6** according to the sequence shown in Scheme 3. Thus, removal of the *tert*-butyl groups in **3d** with TFA afforded the N-benzyloxy derivative **4** of a naturally occurring α-amino acid, 4-methylene (*S*)-glutamic acid.[13] Cyclization in the presence of catalytic PTSA gave N-benzyloxy α-methylene L-pyroglutamic acid **5**.

Scheme 3



In summary, we have developed a method for the enantioselective allylation of α-ketoester oximes with phenyl substituted chiral bis(oxazoline) allylzinc reagents. This method provides an expedient access to enantiomerically pure or highly enriched derivatives of allylglycine, as well as several analogs harboring usable functionality that can be easily transformed into a variety of synthetically useful chirons.[14]

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10. General procedure: To the dry THF(6 mL) solution of phenyl substituted bis(oxazoline)(337 mg, 1.10 mmol) was added *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.10 mmol) at -78°C under Argon. The mixture was stirred for 15 min. at 0°C before the allylzinc bromide(1.00 mmol) was introduced, and the resulting mixture was stirred for another 15 min. The reaction mixture was cooled to -78°C and a solution of O-benzyl oxime of *tert*-butyl glyoxylate **1b** (211 mg, 0.90 mmol) in dry THF(3 mL) was added via cannula at -78°C. After 1h at -78°C, the reaction mixture was quenched with aqueous NH_4Cl solution, extracted with EtOAc, and processed as usual. The residue was purified by chromatography on silica gel (10% EtOAc in hexanes) to afford N-benzyloxy L-allylglycine **3a** (204 mg, 82%, 93%ee).
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