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1, 2-Asymmetric *cis* Induction and its Application to the Asymmetric Synthesis of Precursors of β-Branched Unusual Amino Acids

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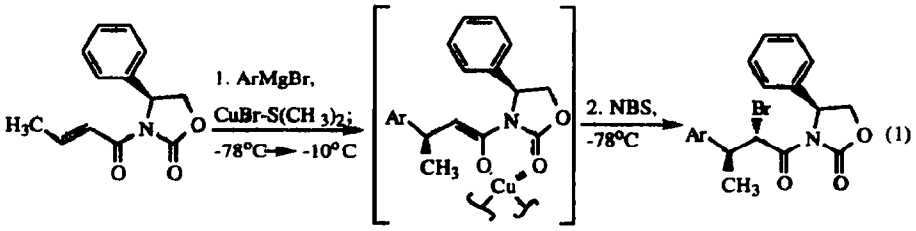
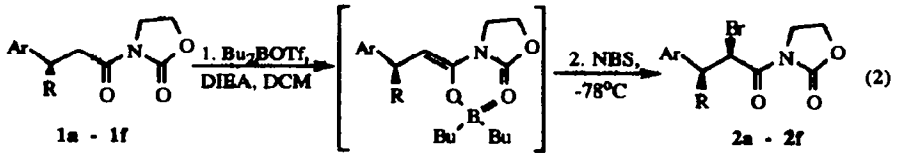
Abstract: A new method for the asymmetric synthesis of key intermediates of unusual amino acids has been established by utilizing β-carbon chirality for asymmetric induction in allylic-strained boron enolates.

The design of receptor-selective peptide and peptidomimetic ligands with highly potent and specific biological properties has become one of the most important areas in bioorganic chemistry, medicinal chemistry, molecular biology and other related research areas.[1,2] We and others have previously proposed and demonstrated the importance of implementing β-branched α-amino acids in the design of biologically active peptide ligands with specific conformational and topographical features.[3] Therefore, extensive development of synthetic organic chemistry of unnatural amino acids has become crucial to the future of these areas.[4-8]

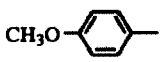
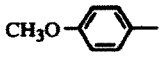
Recently, we have reported a diastereospecific tandem Michael-like addition of a copper enolate followed by an electrophilic bromination, in high optical purity and yield, which leads to *trans* precursors of β-branched α-amino acids when used in conjunction with a modified Evans auxiliary[8a, 9](eq. 1). Both α and β chiral centers were controlled by the chirality of the auxiliary in equation 1. We wish to know the effect of the β chiral center on asymmetric induction at the α center, and to explore its use for the asymmetric synthesis of key intermediates of unnatural amino acids.





Boron enolates of the type derived by using the method of Mukaiyama and colleagues[10] have shown great success in their application to asymmetric synthesis, especially in asymmetric aldol reactions,[11] though only a few cases have been reported that are specifically related to the asymmetric synthesis of amino acids. Evans and coworkers were the first to apply chiral boron enolates to the asymmetric synthesis of α-amino acids[5] in which an oxazolidinone auxiliary was used to control the stereochemistry of the α chiral center with excellent efficiency. In conjunction with our efforts to develop highly systematic approaches to the asymmetric synthesis of unusual amino acids,[7, 8] we report here preliminary results of this new approach in which the chirality of the α-carbon center was induced through the chirality of the β-position of the boron enolate. (eq. 2, corresponding results listed in Table 1).

Table 1. The results of 1, 2-asymmetric *cis* induction (**a-f**)

	Ar	R	Chirality β-carbon **1a-1f**	Ratio *cis/trans* (crude)	Purified yield %	Purified d.e. % @	δ-H_α of **2a-2f**(ppm) (Coupling *Const.* Hz)	$[\alpha]_D^{25}$ ($CHCl_3$)
a		CH_3-	S	7.2 : 1	82	>99	6.00 (10.6)	-6.0 (c=3.5)
b		CH_3-	R	7.3 : 1	67	>99	6.00 (10.6)	+5.8 (c=1.8)
c		CH_3-	S	3.8 : 1	70	>99	5.95 (10.7)	+19.4 (c=1.7)
d#		CH_3-	R	4.0 : 1	66	>99	5.95 (10.7)	-19.1 (c=1.8)
e		CH_3CH_2-	S	3.0 : 1	50	>99	6.06 (11.2)	-10.6 (c=2.2)
f		CH_3CH_2-	R	2.3 : 1	51	>99	6.06 (11.2)	+9.8 (c=2.6)

@ >99% indicates that only one isomer was observed

a single crystal X-ray structure was obtained

The bromination reactions were performed via a procedure similar to that described by literature[5,8d] which is represented by example **a**. A precooled solution of the acyl-oxazolidinone derivative **1a**,[12] 0.600 g, 2.57 mmol) in dry dichloromethane(5.80 ml) was added by diisopropylethylamine (0.630 ml, 3.60 mmol, 1.40 eqv) and dibutylboron triflate (1.0 M solution in dichloromethane, 3.60 ml, 1.40 eqv) at -78 ^{0}C under nitrogen. The resulting light yellow solution was stirred at -78 ^{0}C for 20 min, 0 ^{0}C for 1 h and recooled to -78 ^{0}C before being transferred through a Teflon cannula to a slurry solution of N-bromosuccinimide (0.660 g, 3.70 mmol, 1.40 eqv) in dichloromethane (8.10 ml) at -78 ^{0}C. The resulting brown mixture was stirred at -78 ^{0}C for 2 h and quenched by pouring into 0.5 N aqueous sodium bisulfate. The water phase was extracted three times with ethyl acetate. The combined organic solution was washed twice with 0.5 N aqueous sodium thiosulfate and once with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude residue was evaluated by ^{1}H-NMR prior to column chromatography to yield a pale yellow oil of product **2a** (0.66 g, 82%).

TLC and ^{1}H-NMR (250 MHz) have been found to be a convenient way in order to monitor the reaction progress and determine the stereoselectivities of the resulting bromides (**2a-2f**). The TLC conditions employed were EtOAc:Hexane:CH_3CN (2.7:6.3:1) for reactions **c** and **d**, and EtOAc:Hexane (3:7) for reactions **a, b, e** and **f**. The minor diastereoisomeric compounds were readily separated by silica gel chromatography [E. Merk silica gel 60 (230-400Å)]. Solid products were obtained for **2c** and **2d** which could be easily crystallized. X-ray structure analysis was performed for **2d**. All of the other products remained as viscous pale yellow oils. The down -field chemical shifts of the α-carbon protons of the bromides (**2a-2f**) (doublets, ranging from 5.95 to 6.06 ppm) were used to evaluate the ratios of *cis / trans* product formation by integration.

The stereochemistry of the asymmetric *cis* induction was unequivocally confirmed by single crystal X-ray structure analysis of one of the bromination products (Fig. 1):

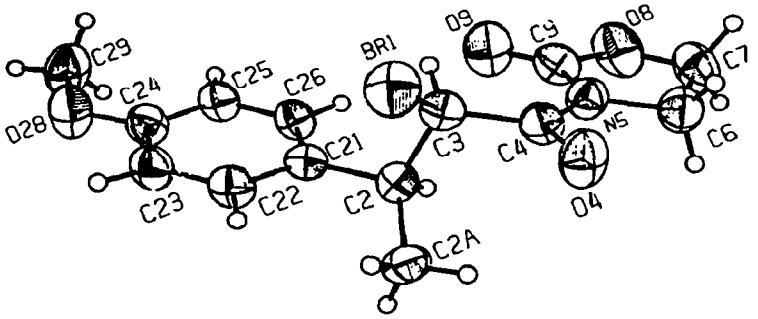


Fig. 1 The X-ray structure of 3(2R, 3S)-[2-bromo-3-(4'-methoxy-2'-methylphenyl)-1-oxopropyl-2-oxazolidinone (**2d**)

It is interesting to note that it is difficult to define precisely the configurational orientation of the allylic system for the β chiral centers in the enolate intermediates that we studied.[8] However, based on the resulting stereochemistry it is reasonable to predict the possible existence of allylic strain effects[13, 14] in these enolates. It is easy to understand the origin of the resulting chirality from the following model of allylic strain effects (Fig. 2). We believe that this is the first documentation of such effects as seen in boron enolates from oxazolidinone derivatives and the first application of an enolate with a strain effect for the asymmetric synthesis of unusual amino acids.

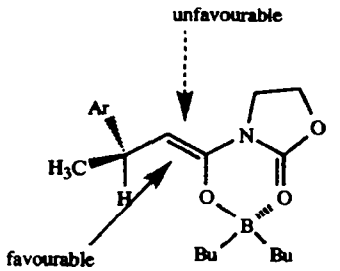


Fig. 2. The stereochemistry of the boron enolate with allylic strain effect

Further examples to elucidate this allylic strain phenomenon are under investigation. Also improvements in the reaction conditions of this new methodology are continuing, and direct conformational studies of enolates by NMR techniques will be investigated in this laboratory.

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