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Diastereoselective Synthesis of β-Heteroaryl *syn*-α-Methyl-β-Amino Acid Derivatives via a Double Chiral Auxiliary Approach

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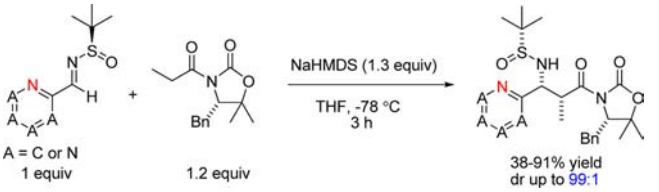
ABSTRACT



The addition of the SuperQuat enolate to five- and six-membered heterocyclic *tert*-butyl sulfinimines led to a high *syn*-selectivity of up to 99:1 in good to excellent yields. The reaction is tentatively proposed to proceed through an open-chain transition state with the presence of an α-heteroatom on the sulfinimine leading to high diastereoselectivities. The adducts were derivatized to β-amino esters and amides in a facile manner.

β-Amino acids are present as key building blocks in bioactive natural products such as taxol and cocaine as well as in naturally occurring peptides such as bestatin and pepstatin.[1] Their derivatives, β-lactams, are prevalent structural motifs in antibiotics.[2] The presence of β-amino acids in polypeptides can potentially enhance their biological activities and physical properties.[3]

In recent years, asymmetric syntheses of β-amino acid derivatives have received much attention from the synthetic community and various methods have been developed to access different substitution patterns.[4] In the context of supporting our internal medicinal chemistry programs, we were particularly interested in the stereoselective synthesis of β-heteroaryl α-substituted-β-amino acid derivatives. Several asymmetric synthetic methods for the preparation of α,β-disubstituted β-amino acid derivatives are known in the literature; for example, Arndt–Eistert homologation through asymmetric Wolff rearrangement on the α-alkyl-α-diazoketone leads to moderate to good diastereoselectivities.[5] Davies[6] and Hawkins[7] independently reported an asymmetric method relying on the Michael addition of chiral amines to β-substituted acrylate derivatives followed by diastereoselective alkylation. Ring opening of α,β-disubstituted β-lactams with predefined stereochemistry provides an alternative approach.[8] Of particular relevance to us is the pseudoephedrine acetamide based enolate addition to prochiral imines from Badía[9] and the seminal work from Ellman[10] and Davis[11] employing a diastereoselective enolate addition to chiral *N*-sulfinyl imines. These two approaches

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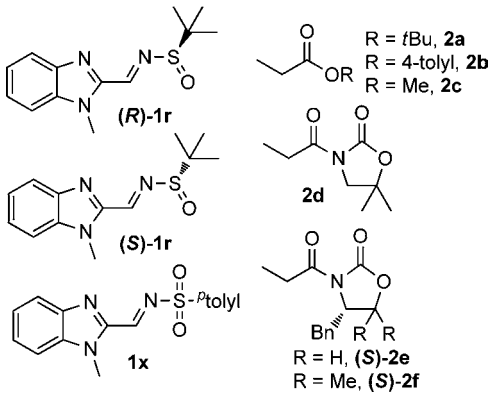
represent a direct and convergent method to construct a C–C bond with good to excellent diastereoselectivities. Among all the approaches, it was noticed that β-substituents were generally limited to alkyl and phenyl groups, and incorporation of nitrogen-containing 2-heteroaryl groups such as 2-pyridyl to the adducts was very rare.[12]

We initiated our investigation following Ellman's enolate addition[10] of simple achiral esters to the 2-benzimidazolyl *tert*-butyl sulfinimine **(*R*)-1r**. Surprisingly, low diastereoselectivity (dr < 2:1) was observed even in the presence of 3 equiv of $ClTi(O^iPr)_3$ (entry 1, Table 1). Screening of different esters gave similarly low diastereoselectivities (entries 2–5). The enolate of **2d**, albeit locked in the *Z*-geometry, did not improve the dr. The observed reversal of facial selectivity from that expected by the chairlike transition state proposed by Ellman[10] and others[9,11] suggests that the presence of an α-heteroatom disrupts such transition states. Such disruption could come from competitive chelation from the α-heteroatom. This chelation effect has been seen in the reversal of stereoselectivity in the Grignard addition to 2-pyridyl[13] and α-alkoxy[14] *tert*-butyl sulfinimines. In our case, it seemed clear that in order to achieve a higher dr, extra stereocontrolling elements were required. We envisioned a second chiral auxiliary from the enolate may enable stereocontrol for the α-center and thus improve the dr. Gratifyingly, a combination of **(*S*)-1r** and Evans' auxiliary[15] **(*S*)-2e** improved the dr to 6:1 (entries 8 and 9). As a comparison, the prochiral *p*-tosylimine **1x** and **(*S*)-2e** (entry 6) gave a lower dr (1:1).[16] This indicated that the stereoselectivity could be modulated by double asymmetric induction.[17] At this stage, we tested out the more sterically demanding Davies' SuperQuat[18] **(*S*)-2f** which has shown certain advantages over Evans' auxiliary. Even in the mismatched case (entry 10), the dr was improved to 10:1 compared to the matched case use of Evans' auxiliary. A matched combination between **(*R*)-1r** and **(*S*)-2f** (entry 11) dramatically enhanced the dr to 99:1. Notably in both cases, the stereochemical outcome for the major diastereomers (**3r** and **3y**, Scheme 1) was equal as proven by the fact that removal of the sulfinyl group led to the identical product **4** (Scheme 1). This illustrated that the SuperQuat is the major controlling element in the addition process.[19] Furthermore, the matched pairing of Evans' auxiliary **(*S*)-2e** and SuperQuat **(*S*)-2f** to the opposite enantiomer **(*S*)-1r** and **(*R*)-1r**

Table 1. Optimization of the Enolate Addition Reactions[a]



entry	imine	enolate	base/additive	dr[d]	yield (%)
1	(*R*)-**1r**	**2a**	LDA/$ClTi(O^iPr)_3$	1.9:1	75[b]
2	(*R*)-**1r**	**2a**	LDA	1.5:1	79[b]
3	(*R*)-**1r**	**2b**	NaHMDS	1.6:1	88[b]
4	(*R*)-**1r**	**2c**	LDA	1.3:1	62[b]
5	(*R*)-**1r**	**2d**	LDA	1.2:1	85[b]
6	**1x**	(*S*)-**2e**	LDA	1:1	77[b]
7	(*R*)-**1r**	(*S*)-**2e**	LDA	2:1	69[b]
8	(*S*)-**1r**	(*S*)-**2e**	LDA	6:1	37[c]
9	(*S*)-**1r**	(*S*)-**2e**	LDA/LiCl	6:1	56[c]
10	(*S*)-**1r**	(*S*)-**2f**	NaHMDS	10:1	76[c]
11	(*R*)-**1r**	(*S*)-**2f**	NaHMDS	99:1	89[c]

[a] All reactions run with 2 equiv of esters/amides in THF at −78 °C for 1–3 h. [b] Combined isolated yield for the mixture of diastereomers. [c] Isolated yield for the major diastereomer. [d] Diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture and/or by HPLC.

Scheme 1. Deprotection

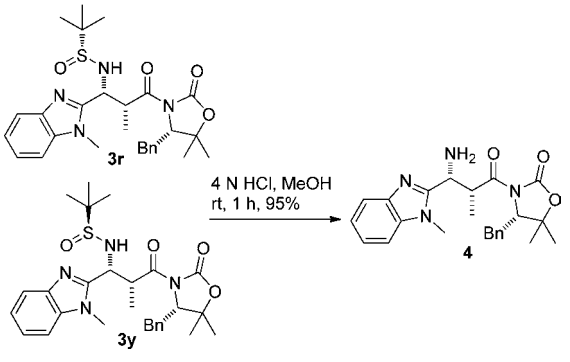


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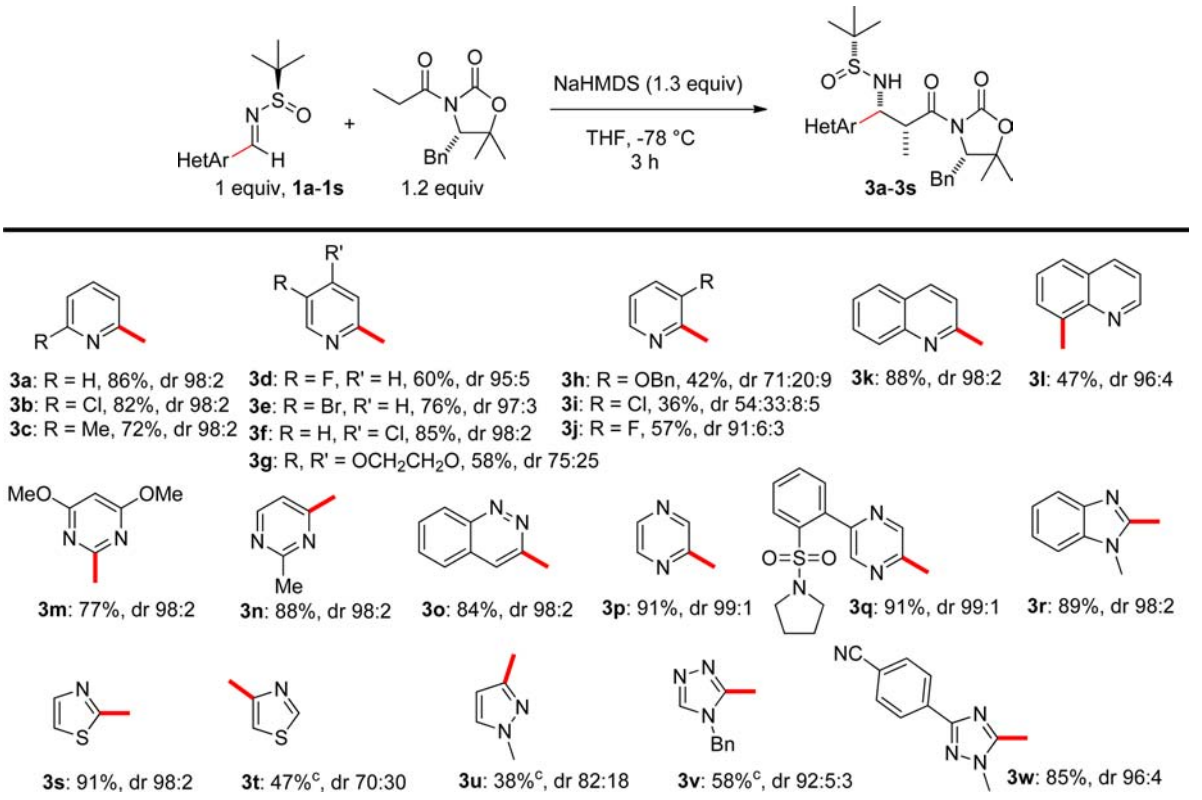
Table 2. Substrate Scope of the SuperQuat Enolate Addition to the Heterocyclic *N*-*tert*-Butanesulfinyl Aldimines[a,b]



[a] All reactions run at 0.2 M in THF at 0.3 mmol scale. [b] If not specified, yields refer to the major diastereomer isolated over silica gel. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture and/or by HPLC. [c] Combined isolated yields of diastereomers.

suggests that the Evans and SuperQuat enolates proceed through a different favored transition state.[19a]

The success of the addition to the first substrate **(*R*)-1r** prompted an investigation into the breadth of this reaction. Further optimization revealed that bases (LDA, LiHMDS, and NaHMDS) did not have a noticeable effect on the dr and yields, suggesting that the potential for chelation control of the reaction was diminished. A slight excess of the SuperQuat (1.2 equiv) was sufficient to drive the reaction to completion within 3 h at −78 °C. Notably, the presence of the α-heteroatom of the aromatic was crucial for achieving excellent dr's and yields. For example, while the addition to the 2-pyridyl substrates provided satisfactory results, the 3-pyridyl counterpart resulted in a low dr (3:1) and yield (41%). Similarly, the SuperQuat enolate addition to phenyl and 4-nitrophenyl *tert*-butyl sulfinimines gave poor dr's (< 2:1) and yields (< 40%).[20]

It was gratifying to find that the conditions discovered for the high *syn*-selective enolate addition reaction translated into the successful addition to a range of five- and six-membered heterocycles. The substrate scope is highlighted in Table 2. For the six-membered heterocycles, pyridines, quinolines, pyrazines, pyridazines, and pyrimidines were investigated. Although the electron-donating and -withdrawing groups at the 6-position of the pyridine ring (**1b** vs **1c**) significantly affect the electron density of the nitrogen,[21] both substrates gave excellent dr's and good yields. For the 5-substituted pyridines, less electron-withdrawing groups (**1d** vs **1e**) provided slightly improved dr's and yields. For the 3-substituted pyridines (**1h**−**1j**), the increased size of the substituent degraded both the diastereoselectivity and the yield. The small F group substituent did, however, give acceptable results. Similarly, the electron-rich poor pyridine substrate (**1g**) may partly result from the steric effect with the fused bulky saturated ring. For the pyrimidines, both 2- and 4-pyrimidinyl substrates (**1m** and **1n**) afforded excellent dr and yields. Compared with **1g**, the 2-pyrimidine counterpart (**1m**) provided decent results probably benefiting from a double α-heteroatom effect (i.e., less steric interactions and/or increased reactivity). Quinolines, pyridazines, and pyrazines all furnished adducts with excellent dr's and good to excellent yields in the absence of *ortho*-substituents. Remarkably, 8-quinolinyl sulfinimine **1l** also provided high stereoselectivity due to the properly oriented *β*-nitrogen. For the five-membered heterocycles, two α-heteroatoms are required to achieve good dr's and yields. As shown in Table 2, **1s**, **1v**, and **1w** have proven to be good substrates due to a double

(20) The possible chairlike transition state involving the SuperQuat *Z*-enolate is sterically unfavorable. See model **D** in Figure 2.

(21) Katritzky, A. R.; Pozharski, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon/Elsevier: 2000; p 178.

α-heteroatom effect, whereas **1t** and **1u** were less successful in terms of both dr's and yields. This suggests that subtle changes in the steric[19a] or electronic[22] component around the sulfinimine disrupt the optimal orientation, thus diminishing the selectivity.

The X-ray crystal structure of the addition product **3p** confirmed the absolute configuration of the adduct and allowed correlation of the *syn*-stereochemistry of the related products (Figure 1).

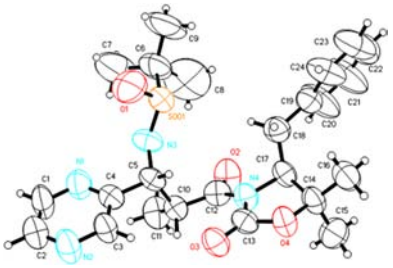


Figure 1. X-ray structure of the pyrazine adduct **3p**.

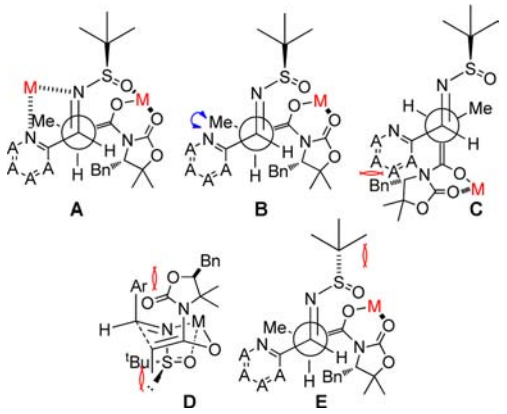
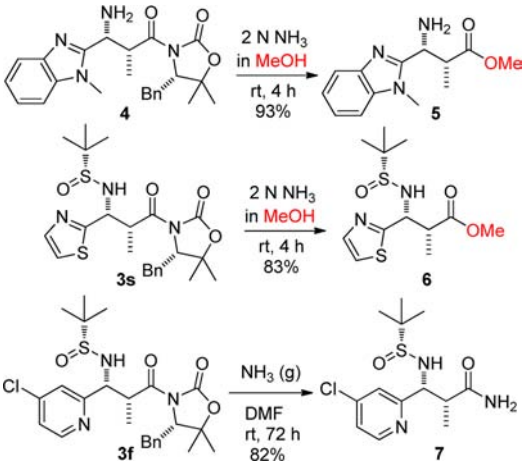


Figure 2. Proposed models.

The absolute stereochemistry could be rationalized by model **A** in Figure 2. The chelation between the two N's and the chelation among the three O's stabilized the conformation to minimize the interaction between the bulky *tert*-butyl group and the benzyl group, thus reinforcing the stereoselectivity. However, it is hard to explain how chelation could be the controlling element with sodium as the counterion. It may therefore be that the chelation between the two N's is unnecessary and high stereoselectivity simply resulted from an open chain model **B**. The increased diastereoselectivity that the α-heteroatom brings may be due to the diminished steric impact from removal of an α C−H. An electronic component to the effect cannot be discounted, and it may be that a repulsion of the α-heteroatom lone pair is important in giving selectivity. Model **C** suffers from the steric repulsion between the heteroaryl and the SuperQuat. The chairlike model **D** is ruled out because it is sterically encumbered and it also leads to the *anti* products. Model **E** explains the mismatched case when (*S*)-*N*-*tert*-butanesulfinyl imine is applied.

With a general method for the stereoselective generation of adducts **3a**−**3w** in hand, attention was turned toward synthesizing β-amino acid derivatives. Owing to the intrinsic benefits offered by the SuperQuat,[23] facile alcoholysis and aminolysis occurred predominantly in the exocyclic mode without losing stereochemical integrity. Treatment of **4** and **3s** with a 2 N solution of NH_3 in MeOH cleanly afforded β-amino methyl ester **5** and **6** after 4 h at rt (Scheme 2). Similarly, β-amino amide **7** was generated slowly with saturated NH_3(g) in DMF. Of further note, the *N*-*tert*-butanesulfinyl group and the SuperQuat can be orthogonally removed, which allows the adducts **3a**−**3w** to be versatile building blocks for peptide syntheses.

Scheme 2. Derivatizations of the Adducts



In summary, an efficient double chiral auxiliary approach was developed to access β-heteroaryl *syn*-α-methyl-β-amino acid derivatives. The enolate addition was tentatively proposed to proceed through an open chain transition state. The current work will enhance options for the asymmetric synthesis of β-amino acids. Future work will involve examining the scope of α-substituents and epimerizing the α-center to access *anti*-β-amino acid derivatives and will be reported in due course.

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Supporting Information Available. Experimental procedures, compound characterization data, NMR spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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