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Highly Enantioselective and Diastereoselective Synthesis of β-Amino Acid Esters and β-Lactams from Achiral Esters and Imines

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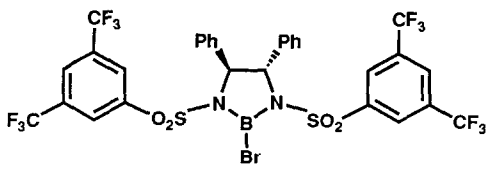
Summary: *The reaction of S-tert-butyl thiopropionate with a number of N-benzyl or N-allyl aldimines (**4**) as promoted by the chiral diazaborolidine **1** and triethylamine afforded the β-amino acid esters **5** with high diastereoselectivity and enantioselectivity, providing a simple route to chiral β-lactams **6**.*

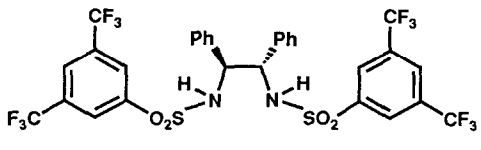
The condensation of imines with ester enolates to form β-lactams is an important route to this structural class which has been extended beyond the original Gilman-Speeter version (involving zinc enolates)[1] to boron,[2] lithium,[3] aluminum,[4] and tin[5] enolates. Recently a number of groups have described the stereoselective synthesis of chiral β-lactams by reactions in which either the imine[5b,6] or ester[3b,7] component is chiral. We report herein the first method for the asymmetric synthesis of chiral β-amino acid esters and β-lactams from *achiral* imines and esters using the chiral organoboron reagent **1**.[8] This and related reagents have been used successfully in enantioselective Diels-Alder,[9] aldol,[8,9] carbonyl allylation,[10] carbonyl propargylation,[11] olefin bis-hydroxylation,[12] Ireland-Claisen rearrangement[13] and Darzens[14] reactions.[15] The chiral controller group **2** from which reagent **1** is derived (by reaction with BBr_3) is readily separated from the β-amino acid ester for reuse.

As previously reported,[8] the reaction of the *S,S*-diazaborolidine **1** with *S-tert*-butyl thiopropionate with triethylamine in toluene–hexane at -78 ° produces the "transoid" boron enolate **3** (Scheme 1). Reaction of **3** at -78 ° with the *N*-benzyl or *N*-allyl imines of a variety of aldehydes (**4**) proceeded with high diastereoselectivity and high enantioselectivity to form mainly the β-amino acid esters **5**. Treatment of the β-amino acid esters **5** with *tert*-butylmagnesium chloride in ether at -78 ° to 20 ° resulted in ring closure to form the *trans*-α,β-disubstituted β-lactams **6**. The *trans* arrangement of the α,β-substituents of **6** was indicated by the ^1H NMR coupling constants ($J_{\alpha\beta}$), observed in each case to be 2 Hz. The experimental results for seven substrates are summarized in Table 1.

In each case the major products **5** and **6** were readily purified by chromatography on silica gel. Enantioselectivities were determined in most cases by HPLC analysis using Daicel chiral columns as

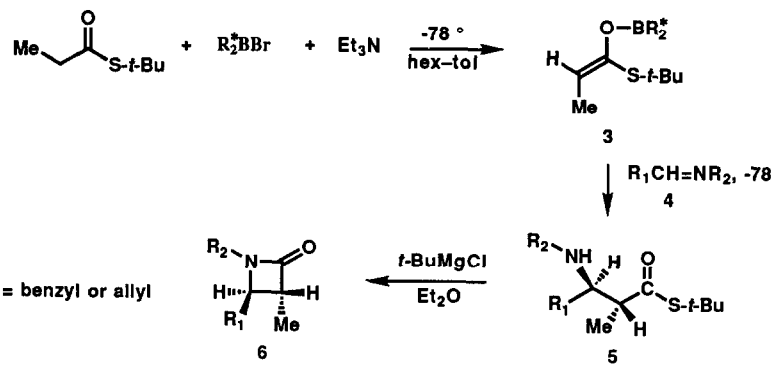


1 (R^*_2BBr)

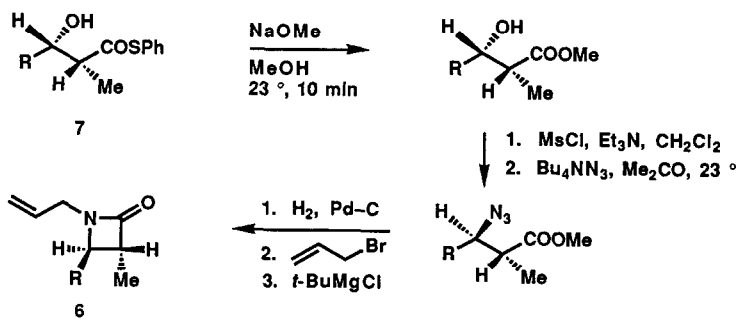


2

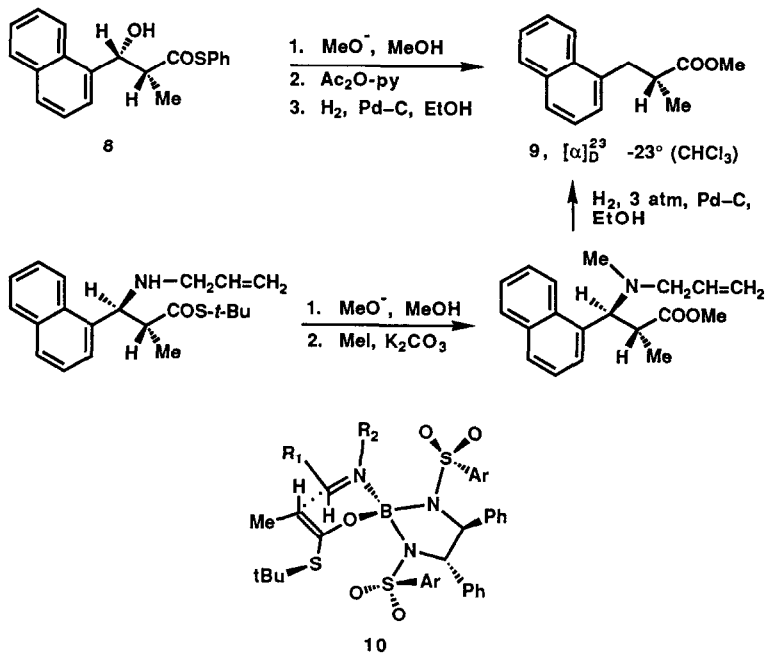
Scheme 1



Scheme 2



Scheme 3



10

indicated in Table 1.[16,17] HPLC or ^{1}H NMR measurements of MTPA derivatives of the primary alcohol corresponding to **5** gave ee values in agreement (±0.5%) with the Daicel column measurements.[16] The absolute configuration of each product was determined by chemical correlation as summarized below.

The *N*-allyl β-lactams **6**, $R_1 = PhCH_2CH_2$, and **6**, $R_1 = PhCH{=}CH$, (Table 1, entries e and f) were correlated with one another by catalytic hydrogenation of the double bonds (H_2, 1 atm, Pd–C, EtOAc, 23 °, 0.5 h) to give the same dextrorotatory β-lactam (**6** $R_1 = PhCH_2CH_2$, $R_2 = CH_3CH_2CH_2$). β-Lactam **6**, $R_1 = PhCH_2CH_2$, R_2 = allyl (dextro form) was synthesized from the known β-hydroxy ester **7**, $R = PhCH_2CH_2$, (prepared as described in ref. 8 with the *S,S* enantiomer of **1**) as shown in Scheme 2, thus proving the absolute configuration. This same method of synthesis was used to convert β-hydroxy ester **7**, R = Ph, and **7**, R = β-naphthyl to the corresponding β-lactams **6**, R = Ph, and **6**, R = β-naphthyl, (dextro forms). The *N*-benzyl β-lactams of entries b and g in Table 1 were also correlated with the corresponding β-hydroxy esters **7** as shown in Scheme 2, except for the use of benzyl bromide for the *N*-substitution step. The remaining β-lactam **6**, R_1 = 1-naphthyl, $R_2 = H_2C{=}CHCH_2$, was correlated with β-hydroxy ester **8**[18] as shown in Scheme 3.

The removal of the *N*-allyl or *N*-benzyl protecting group from β-lactams **6** by standard methods[19] provides access to chiral β-lactams with a wide variety of *N*-substituents. Since the *R,R*-enantiomer of **1** is readily available, the enantiomeric forms of the β-lactams **6** can be produced equally well by the present methodology. Another important advantage of this process for the synthesis of chiral β-lactams derives from the ready separability of the β-amino acid esters **5** and the chiral controller group **2**, which allows efficient recycling of the latter. General experimental procedures for this synthesis of chiral β-amino acid esters[20,21] and β-lactams[22] are provided.

The enantioselective formation of the β-amino acid esters **5** from the *S,S*-diazaborolidine **1** would appear to be a consequence of three factors: (1) The thermodynamically less favorable *Z*-isomer of the aldimine component preferentially complexes with boron enolate **3** for steric reasons. (2) The condensation proceeds preferentially via a chair-like 6-membered transition state. (3) The transition state assembly represented by **10** is preferred for steric reasons over the other chair-like arrangement.

In conclusion, the methodology described herein provides a novel and useful route to many chiral β-lactams.[23]

Table 1

Imine 4			β-Amino Thioester 5				β-Lactam 6		
Entry	R^1	R^2	Time[a]	Yield	$[\alpha]_D^{23}$	anti/syn[b]	Yield	$[\alpha]_D^{23}$	ee
a	phenyl	allyl	10 min	74%	-62.4	> 99 1	92%	+13 9	90[c]
b	phenyl	benzyl	10 min	72	-74.8	> 99.1	96	-12 5	92[c]
c	1-naphthyl	allyl	10 min	77	-56.2	> 99 1	91	-165.0	>99[d]
d	2-naphthyl	allyl	30 min	70	-84.5	> 99:1	94	+2.0	95[e]
e	cinnamyl	allyl	10 min	76	-30 5	> 99.1	86	+29.5	>99[d]
f	hydrocinnamyl	allyl	6 h	67	-45 9	97.3	90	+18 7	90[f]
g	hydrocinnamyl	benzyl	6 h	74	-37.8	92 8	86	+22 0	90[e]

[a] For reaction of 3 and 4 [b] Determined by HPLC analysis on a silica gel column. [c] Determined by conversion to the α-methoxy-α-(trifluoromethyl)phenylacetic ester of 2-methyl-3-(R_2-amino)-3-phenyl-1-propanol and both ^{1}H NMR and HPLC analysis (identical results). [d] Determined by HPLC using a Daicel OJ column, 2 5% *i*-PrOH–hexane [e] Determined by HPLC using a Daicel AS column, 2 5% *i*-PrOH–hexane [f] Determined by HPLC using a Daicel AD column, 2.5% *i*-PrOH–hexane.

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16. Satisfactory ^{1}H NMR, mass and infrared spectral data were obtained for each product.
17. Racemic mixtures were used to demonstrate discrimination between enantiomers.
18. Prepared from 1-naphthaldehyde and *S*-phenyl thiopropionate by the procedure of ref. 8 in 92% yield and >94% de using the *S,S* enantiomer of **1**.
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20. **Imines** were prepared by slow addition of the aldehyde to one equivalent of either allylamine or benzylamine and anhydrous $MgSO_4$ (1 g/mmole) at 22 °, stirring for 5 h and distillation *in vacuo*:
21. **β-Amino Acid Ester Synthesis:** The (-)-*bis*-3,5-di(trifluoromethyl)benzenesulfonamide **2** (300 mg, 0.39 mmol) was placed in a 50 ml round bottomed flask equipped with magnetic stir bar and sealed with a septum. The flask was evacuated and flushed with N_2 three times; all solvents were dry. Dichloromethane (6 ml) was added and the homogeneous solution was treated with boron tribromide (780 µl, 1M in CH_2Cl_2, 0.78 mmol). The solution was warmed to 45 ° and stirred for 3 h and concentrated at 1 mm Hg. Dichloromethane (2 ml) was added and evaporated a second time, to leave a white solid. Toluene (8 ml) was added and the resulting mixture was warmed to dissolve the white bromoborane complex. Hexane (16 ml) was added and the solution was cooled to -78 °, treated with *S-tert*-butyl thiopropionate (62 µl, 0.39 mmol), and stirred for 5 min. Triethylamine (60 µl, 0.43 mmol) was then added and the solution was stirred for 3 h at -78 °. The imine (0.39 mmol) in 1 ml of toluene (cooled to -78 °) was added via cannula over 10 min and the reaction was allowed to proceed for the time indicated in Table 1. Cold methanol was added to the reaction mixture at -78 ° and the solution was brought to 0 °. The β-amino acid ester and bis-sulfonamide were separated extractively and the ester was purified by chromatography on silica gel.
22. **β-Lactam Synthesis:** The β-aminothioester (0.1 mmol), dissolved in 0.5 ml anhydrous ether, was cooled to -78 ° under nitrogen *tert*-Butylmagnesium chloride (0.2 mmol, 110 µl, 1.81 M solution in ether) was added at -78 ° and the solution was stirred for 10 min, after which time the cooling bath was removed. A white precipitate was observed on warming. After stirring at 23 ° for 3 h, the solution was diluted with ether and pH 7 phosphate buffer. The crude β-lactam from the ethereal extract was purified by chromatography on silica gel using 20% ether in hexane for elution.
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