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A highly stereoselective synthesis of indolyl *N*-substituted glycines

Biao Jiang,[a,*] Cai-Guang Yang[a] and Xiao-Hui Gu[b]

[a]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China*
[b]*Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, 115 Mill Street, Belmont, MA 02478-9106, USA*

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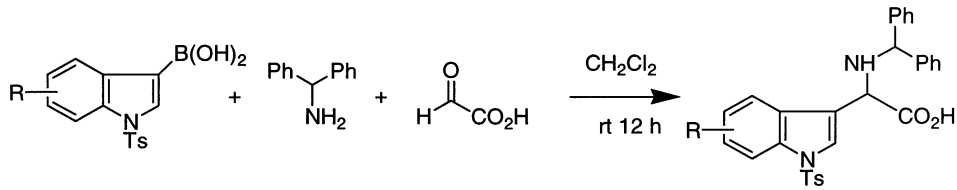
Abstract—Optically active α-indolyl *N*-substituted glycines were synthesized by reaction of an indolyl boronic acid with glyoxylic acid using chiral methylbenzylamine as the chiral auxiliary with high diastereoselectivity. The absolute configuration of the product was determined by a single-crystal X-ray analysis.

Much attention has been paid to the search for concise and flexible methods leading to the formation of optically active amino acids due to their significant biological activities.[1] Indolylglycine derivatives are one of the non-proteinogenic amino acids important in new drug discovery.[2] Optically pure indolylglycines have been used in the synthesis of potent antibiotics of the cephalosporin type,[3] however, there are few reports on the asymmetric synthesis of indolylglycines. A major challenge in the synthesis of indolylglycines is the facile base-catalyzed epimerization which makes it difficult to prepare optically pure indolylglycines.[4] The presently known methods, such as the asymmetric Strecker synthesis,[5] cannot be employed to prepare these molecules due to the products being very unstable, easily reverting to the starting materials.[6] Johannsen reported the synthesis of optically active ethyl 3-indolyl-*N*-tosyl glycinate using a complex of copper(I) salts and Tol-BINAP to catalyze the enantioselective addition of *N*-tosylimino esters of ethyl glyoxylate to indole. This Lectka system[7] required low temperature and critical oxygen and moisture free conditions.[8] In this communication, we wish to describe a concise, and highly diastereoselective synthesis of optically active 3-indolyl-*N*-substituted glycines via a chiral amine-mediated 3-indolylboronic acid Mannich reaction.

Recently a new practical approach to unsaturated amino acids, by reaction of alkenyl boronic acids with glyoxylic acids and amines, was reported by Petasis.[9] This prompted us to investigate the stereocontrolled synthesis of indolyl glycines by the reaction of indolyl-3-boronic acids. To test the reactivity of indolyl boronic acids with an amine and glyoxylic acid, the synthesis of racemic indolyl glycines was first studied. After mixing the three components, *N*-tosyl-3-indolylboronic acid **1**,



1 R = H
2 R = 5-OBn
3 R = 5-Br
4 R = 6-Br

5 R = H 94%
6 R = 5-OBn 91%
7 R = 5-Br 93%
8 R = 6-Br 90%

Scheme 1.

Keywords: indolyl boronic acid; indolylglycine; stereoselectivity.
* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail: jiangb@pub.sioc.ac.cn

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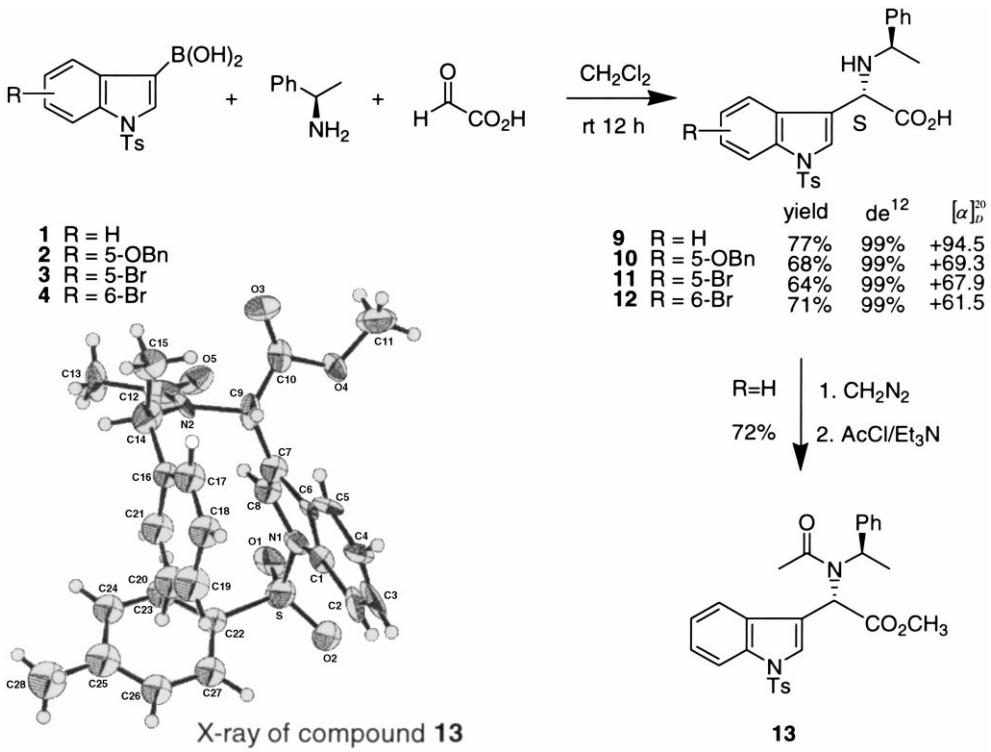

Scheme 2.

aminodiphenylmethane and glyoxylic acid monohydrate in dichloromethane and stirring the mixture at ambient temperature for 12 h, we were able to isolate indolyl glycine **5**, in 94% yield, simply by filtering the insoluble product from the reaction mixture. Further examination of the reaction of indolylboronic acids bearing indole ring substrates **2**–**4**, demonstrated that all of the reactions gave the desired products **6**–**8** in excellent yields (Scheme 1). It was noteworthy that this process does not require anhydrous or oxygen-free conditions. The insolubility of the products in the reaction solvent makes for a very simple isolation procedure.

With the above results in mind, our attention turned to the asymmetric synthesis of indolylglycines using a chiral amine as substrate. The reaction of *N*-tosyl-3-indolylboronic acid **1**, glyoxylic acid and (*R*)-α-methylbenzylamine at room temperature for 24 h in dichloromethane gave the crude product **9** which could be crystallized from methanol to afford a single diastereoisomer in 99% de and 77% chemical yield. To determine the stereochemistry at the α-carbon of compound **9**, the indolyl glycine **9** was converted into its methyl ester with diazomethane and the amino group in the glycine moiety masked with an acetyl group to afford **13** in 72% yield. The X-ray structure analysis of a single crystal of **13** revealed that the absolute configuration at the α-carbon of **13** was *S*.[10] Thus, use of (*R*)-α-methylbenzylamine as the chiral auxiliary created the *S* configuration of the indolyl glycine **11** with a specific rotation of +68, while (*S*)-α-methylbenzylamine gave the *R* enantiomer with a specific rotation of −68 in 99% de and 64% yield. To test the scope of the reaction, a variety of substituted indolyl boronic acids **2**–**4** were screened. As shown in Scheme 2, all the reactions gave the (*S*)-indolyl-*N*-substituted glycines, stereoselectively with 99% de[11,12] in good yields.

In conclusion, the reaction of indolyl boronic acids, chiral amines, and glyoxylic acid monohydrate provides a highly efficient stereoselective synthesis of indolyl *N*-substituted glycines in optically pure form. The present one-pot synthesis of indolyl *N*-substituted glycines has the advantage of mild reaction conditions, readily available reagents and simple product isolation.

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10. X-Ray analysis of **13**: The crystal used for the X-ray study had the dimensions 0.20×0.20×0.30 mm. Crystal data: $C_{28}H_{28}N_2O_5S$, M 504.60; orthorhombic; space group, $P2_1$; lattice parameters, $a=11.323(3)$, $b=27.501(7)$, $c=8.212(4)$ Å; $V=2557(1)$ Å^3, $Z=4$; $D_{calcd}=1.310$ g/cm^3; $F_0=1064.00$; number of reflections measured = 2562, $\lambda=0.7109$ Å.
11. All compounds gave satisfactory spectral data. Representative experimental procedure: To a solution of indolyl boronic acid **1** (316 mg, 1 mmol) in CH_2Cl_2 (8 mL), was added glyoxylic acid monohydrate (92 mg, 1 mmol), followed by (*R*)-methylbenzylamine (121 mg, 1 mmol). The reaction mixture was stirred vigorously at room temperature for 24 h. Upon evaporation of the solvent, the resulting crude product was crystallized from methanol to afford **9** in 77% yield. After product **9** was methylated with diazomethane, the diastereoselectivity was determined by HPLC on OD-H column in 99%. Selected data for compound **9**: $[\alpha]_D^{20}$ +94.5 (*c* 0.825, $CHCl_3$); FTIR (KBr) ν_{max} 3340, 2959, 1739, 1598, 1448, 1373, 1175, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, $J=6.6$ Hz, 3H), 2.33 (s, 3H), 3.55 (q, $J=6.6$ Hz, 1H), 4.44 (s, 1H), 7.16–7.34 (m, 9H), 7.44 (s, 1H), 7.61 (d, $J=7.9$ Hz, 1H), 7.77 (d, $J=8.3$ Hz, 2H), 7.99 (d, $J=8.3$ Hz, 1H); anal. calcd for $C_{25}H_{24}N_2O_4S$: C, 66.96; H, 5.36; N 6.25. Found: C, 67.14; H, 5.47; N, 6.09.
12. Diastereoselectivity of the methyl esters were determined by HPLC on Chiralcel OD-H or OJ-H column with eluted solvent.