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Asymmetric Synthesis of Protected Arylglycines by Rhodium-Catalyzed Addition of Arylboronic Acids to *N*-*tert*-Butanesulfinyl Imino Esters

Melissa A. Beenen, Daniel J. Weix, and Jonathan A. Ellman*

Department of Chemistry, University of California, Berkeley, California 94720

Received January 23, 2006; E-mail: jellman@berkeley.edu

Arylglycines are components of a number of significant drugs, including glycopeptide antibiotics, such as vancomycin,[1] many β-lactam antibiotics, such as cefprozil,[2] and the cardiovascular agent plavix.[3] The synthesis of arylglycines is therefore an important goal in organic chemistry.[4] The addition of arylboronic acids to imino acids via the Petasis reaction is a powerful method for arylglycine synthesis[5] because it capitalizes on the commercial availability of a large number of diverse arylboronic acids displaying a wide array of functionality. However, electron-deficient arylboronic acids are not effective coupling partners, and, to our knowledge, an asymmetric variant of this methodology has not been developed.[6] Herein we report an efficient asymmetric synthesis of arylglycines based on the rhodium-catalyzed addition of arylboronic acids to *N*-sulfinyl iminoacetates, which proceeds in high yields and with very high diastereoselectivity for both electron-rich and -poor arylboronic acid derivatives. We further report on the synthetic versatility of the *N*-sulfinyl arylglycine products in subsequent transformations, including peptide coupling reactions.

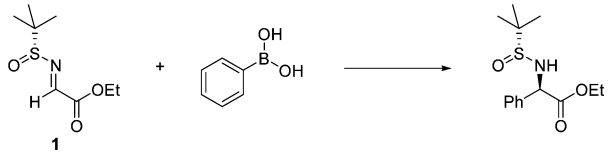
The asymmetric rhodium-catalyzed addition of arylboronic acids to *N*-sulfonyl,[7] *N*-diphenylphosphinoyl,[8] and *N*-sulfinyl imines[8,9] has recently been developed. However, the addition of arylboronic acids to imino esters has yet to be described, presumably because the presence of metal hydroxides, and, under some reaction conditions, water, is not compatible with highly electrophilic imino esters.[10] *N*-Sulfinyl imino esters stand out as stable, isolable compounds that can even be chromatographed on SiO_2 making them excellent starting materials for arylglycine synthesis.[11]

The reported reaction conditions for rhodium-catalyzed arylboronic acid additions to *N*-*tert*-butanesulfinyl imines were first examined using ethyl imino ester **1** (Table 1). A high yield and diastereomeric ratio were observed using dioxane as solvent and a rhodium 1,2-bis(diphenylphosphinyl)benzene complex as the catalyst (entry 1).[8] In contrast, a poor yield occurred under ligand-free conditions with water as a cosolvent due to competitive imine hydrolysis (entry 2).[9] Because Et_3N has been reported to accelerate the rhodium-catalyzed additions to imines in water,[9] this base was also added to the reaction conducted in dioxane (entry 3). Although the reaction proceeded to high conversion, a loss of diastereoselectivity was observed due to base-mediated epimerization of the product. A control reaction was also performed to demonstrate that without the rhodium catalyst no reaction occurred (entry 4).

With optimal reaction conditions identified, a survey of different esters[11] was next carried out (Table 2). Additions to the methyl, benzyl, and *tert*-butyl esters **2**−**4** all proceeded in high yields and with excellent diastereoselectivity, providing a high degree of flexibility in the choice of ester protecting groups. Methyl ester **2** was selected for further investigation of the scope of the reaction with respect to the arylboronic acid.

We were pleased to discover that the methodology is tolerant of many functional groups (Table 3). Similar to the Petasis reaction, high yields were achieved when an electron-donating substituent

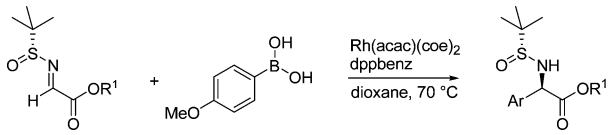
Table 1. Reaction Optimization



entry	catalyst/base	temp (°C)	yield (%)[a]	dr[b]
1	Rh(acac)(coe)$_2$, dppbenz[c]	70	89	97:3
2[d]	[Rh(cod)(CH$_3$CN)$_2$]BF$_4$, Et$_3$N	rt	6	91:9
3	Rh(acac)(coe)$_2$, dppbenz, Et$_3$N	70	92	82:18
4	none	70	0	

[a] Isolated yields after column chromatography. [b] See Supporting Information for diastereoselectivity determination. [c] dppbenz = 1,2-bis(diphenylphosphinyl)benzene. [d] Reaction conducted in 1:2 dioxane:H_2O as described in ref 9.

Table 2. Evaluation of Ester Protecting Groups



entry	imino ester	R^1	yield (%)[a]	dr[b]
1	**1**	Et	89	98:2
2	**2**	Me	89	99:1
3	**3**	Bn	85	98:2
4	**4**	*t*-Bu	78	98:2

[a] Isolated yields after column chromatography. [b] See Supporting Information for diastereoselectivity determination.

was present on the aryl ring of the boronic acid (Table 3, entries 1−3). While sterically hindered ortho-substituted aryl rings proved problematic for this same catalyst in our previously reported arylboronic acid addition to aldimines,[8] *o*-tolylboronic acid was successfully incorporated into the arylglycine product (entry 3). Electron-neutral substituents were also tolerated (entry 4). Given the lack of success achieved with electron-deficient arylboronic acids in the Petasis reaction,[5,6] we were most interested in evaluating the preparation of electron-deficient arylglycine derivatives. Both weakly and strongly electron-withdrawing substituents on the aryl rings gave good yields of desired product (entries 5−8). However, no reaction was observed when a 3-pyridylboronic acid was subjected to our optimized reaction conditions (entry 9). Throughout this series of experiments, we were very pleased to find that the addition of all types of arylboronic acids proceeded with high levels of diastereoselectivity (≥98:2).

A key feature of this arylglycine synthesis method is the versatility of the *N*-sulfinyl-α-amino ester products **5** in subsequent transformations. Selective cleavage of the sulfinyl group or ester

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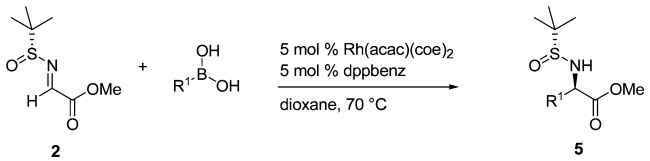
Table 3. Synthesis of Functionalized Arylglycines

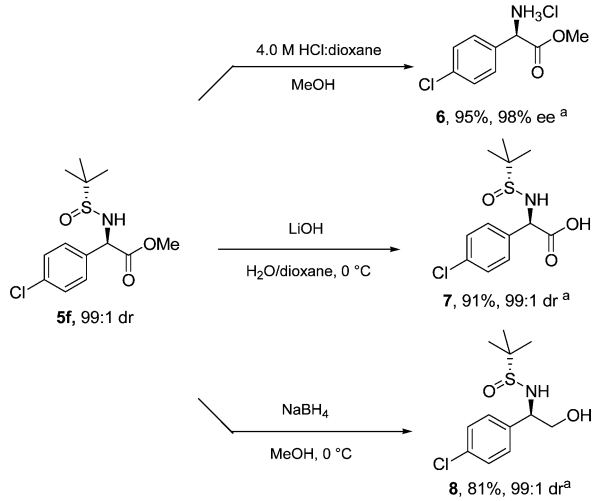


2 **5**

entry	R^1	product	yield (%)[a]	dr[b]
1	4-methoxyphenyl[c]	**5a**	89	99:1
2	*para*-tolyl	**5b**	90	98:2
3	*ortho*-tolyl	**5c**	61	99:1
4	Ph[c]	**5d**	79	99:1
5	3-acetylphenyl	**5e**	87	99:1
6	4-chlorophenyl[c]	**5f**	82	99:1
7	4-trifluoromethylphenyl	**5g**	74	98.5:1.5
8	3-(NO_2)-phenyl	**5h**	69	99:1
9	3-pyridinyl	**5i**	0	

[a] Isolated yields after column chromatography. [b] See Supporting Information for diastereoselectivity determination. [c] Absolute configuration was determined by comparing the optical rotation of the corresponding free amino ester to those reported in the literature (see Supporting Information).

Scheme 1. Selective Functional Group Transformations[a]



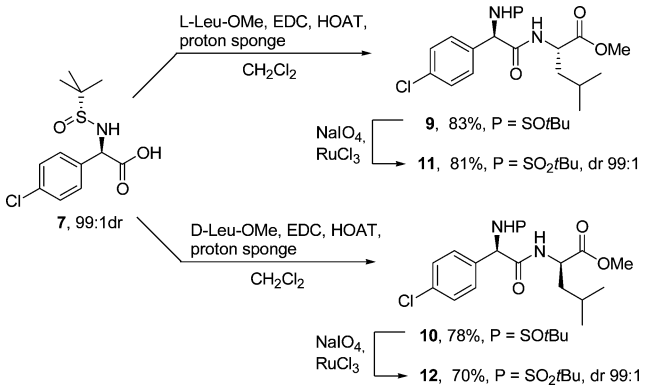
[a] See Supporting Information for determination of enantiomeric and diastereomeric purity.

can be accomplished in high yields with no loss in stereochemical purity (Scheme 1). In addition, straightforward conversion of amino esters **5** to β-amino alcohols can be achieved using $NaBH_4$.

The applicability of the *N*-sulfinyl-α-amino acids as protected amino acid derivatives in peptide synthesis was also demonstrated for the first time.[12] Using coupling conditions developed by Carpino,[13] *N*-sulfinyl amino acid **7** was successfully coupled to both the *R*- and *S*-leucine methyl ester in good yields (Scheme 2). Moreover, despite the acidity of the α-proton in arylglycines, little to no epimerization was observed for either coupling reaction as determined by HPLC analysis of the diastereomeric products **11** and **12** prepared by oxidation of the sulfinyl group in coupling products **9** and **10**.[14]

In summary, an efficient and highly diastereoselective synthesis of arylglycines has been developed that allows incorporation of electronically and sterically diverse arylboronic acids. The *N*-sulfinyl

Scheme 2. Peptide Coupling of *N*-Sulfinyl-Protected Arylglycines



arylglycine products are also versatile synthetic intermediates for further transformations, including selective protecting group removal, conversion to β-amino alcohols and direct incorporation into peptides, with each transformation proceeding in good yields with minimal to no racemization.

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

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