DOI: 10.1002/adsc.200700362

# Palladium(II)-Catalyzed One-Pot Enantioselective Synthesis of Arylglycine Derivatives from Ethyl Glyoxylate, *p*-Toluenesulfonyl Isocyanate and Arylboronic Acids

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Received: July 24, 2007; Revised: November 20, 2007; Published online: January 4, 2008

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

**Abstract:** A palladium(II)-catalyzed, one-pot enantioselective synthesis of arylglycine derivatives from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate and arylboronic acids giving moderate to good yields and enantioselectivity has been developed. This reaction provides a convenient and efficient method for the synthesis of arylglycines.

**Keywords:** arylboronic acids; arylglycines; enantioselectivity; one-pot reaction; palladium

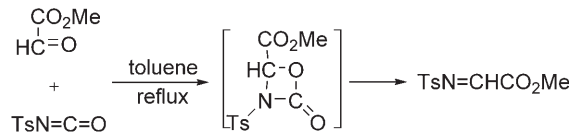
As a non-proteinogenic class of amino acids, arylglycines are applied extensively in drugs, many β-lactam antibiotics, and cardiovascular agents.[1] The synthesis of optically active arylglycines has received much attention[1,2] and the application of asymmetric catalysis towards the formation of these compounds is a fundamental challenge.[3,4]

Ellman reported a diastereoselective synthesis of arylglycine derivatives by the rhodium-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinylimino esters,[5] which proceeds in high yields with very high diastereoselectivity for both electron-rich and electron-poor arylboronic acids. Recently, we reported a similar work using cationic palladium catalysis.[6] However, to the best of our knowledge, there is no report about a catalytic enantioselective synthesis of arylglycines based on the transition metal-catalyzed addition of arylboronic acids to imino acids or esters. Herein, we report a palladium(II)-catalyzed, one-pot enantioselective synthesis of arylglycine derivatives from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate and arylboronic acids that gives moderate to good yields and enantioselectivity.

Imino esters are excellent electrophilic substrates for the synthesis of the optically enriched α- and β-amino acid derivatives and β-lactams.[7] Holmes reported the preparation of imino esters by the thermal [2+2]cycloaddition of *p*-toluenesulfonyl isocyanate and methyl glyoxylate (Scheme 1).[8] The reaction took place in refluxing toluene to give a solution of the imino ester which was at least 80% pure as judged by $^1$H NMR, and could be used *in situ* in subsequent reactions. It occurred to us that it should be possible to combine the synthesis of the imino esters and Pd(II)-catalyzed enantioselective synthesis of arylglycines in one-pot to enhance the synthetic efficiency.

Our group has recently reported the Pd(II)-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds[9] and the addition of arylboronic acids to nitriles.[10] It was found that the ligand 2,2′-bipyridine (bpy) is crucial in these reactions. The presence of the bpy ligand in these reactions might influence the arylpalladium species from being electrophilic to being more nucleophilic, making the above addition reactions possible. It occurred to us that bpy may also be useful in the addition reaction of arylboronic acids to imines catalyzed by Pd(II) species.

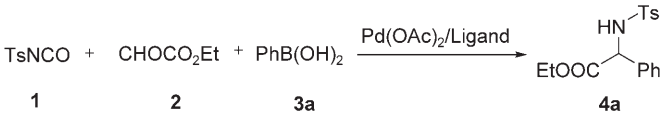
Initially, we investigated the reaction of *p*-toluenesulfonyl isocyanate (**1**) (0.355 mmol) with ethyl glyoxylate (**2**) (0.355 mmol) in refluxing toluene (2 mL) for two days, after which $Pd(OAc)_2$ (5 mol%), 2,2′-bipyridine (bpy, 6 mol%) and phenylboronic acid (**3a**) (0.71 mmol) were added. To our delight, the reaction

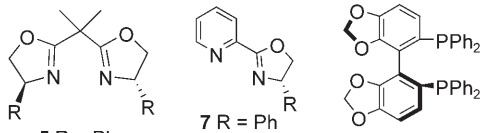



**Scheme 1.** Formation of imino esters from *p*-toluenesulfonyl isocyanate and methyl glyoxylate.

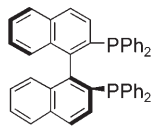
**Table 1.** Screening of the ligands.[a]

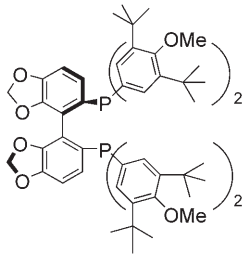









| Entry | Ligand | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | bpy | 53 | - |
| 2 | **5** | trace | - |
| 3 | **6** | trace | - |
| 4 | **7** | 42 | 37 |
| 5 | **8** | 45 | 48 |
| 6 | **9** | 51 | 80 |
| 7 | **10** | NR | - |
| 8 | **11** | NR | - |
| 9 | **12** | trace | - |

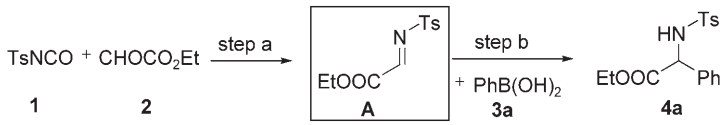
[a] *Reaction conditions:* **1** (0.355 mmol) and **2** (0.355 mmol) in refluxing toluene (2 mL) for two days, then $Pd(OAc)_2$ (5 mol%), ligand (6 mol%) and **3a** (0.71 mmol) were added with refluxing for additional 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a Chiralcel column.

proceeded to yield the addition product **4a** in 53% yield after refluxing for additional 24 h (Table 1, entry 1).

To achieve the asymmetric addition, we screened some homochiral nitrogen-containing and diphosphine ligands instead of the bpy as shown in Table 1. We initially employed the easily available monooxazoline (pymox) and bisoxazoline as ligands. When bisoxazoline was used, no addition products were obtained (Table 1, entries 2 and 3). When using the pymox instead of the bpy ligand, the reaction did proceed smoothly. It was found that the different substituents on the oxazoline ring significantly affected the enantioselectivity of the reaction (Table 1, entries 4–6). The employment of (*S*)-pymox-Bn (**9**) as the ligand led to the highest enantioselectivity (up to 80% *ee*). Upon use of diphosphines as the ligand, no addition product was formed (Table 1, entries 7–9).

With these results in hand, further efforts to improve the yield were made. In our reaction, the time of first step (step a) could be shortened by the addition of a catalytic amount of $AlCl_3$.[11] First, we investigated the reaction of **1** (0.355 mmol), **2** (0.355 mmol) and $AlCl_3$ (10 mol%) in refluxing toluene (2 mL) for 3 h, after which the $Pd(OAc)_2$ (5 mol%), ligand **9** (6 mol%) and **3a** (0.71 mmol) were added. Unfortunately no addition product was formed (Table 2, entry 2). In view of the strong Lewis acidity of cationic Pd(II) complexes,[12] $Pd(CF_3CO_2)_2$ was used instead of the $AlCl_3$ and $Pd(OAc)_2$, but the same result was obtained (Table 2, entry 3). When the combination of $Pd(CF_3CO_2)_2$ and ligand **9** was used, a satisfactory result (65% yield and 76% *ee*) was obtained (Table 2, entry 4). Limited improvement was made by utilizing $Pd(OAc)_2$ instead of $Pd(CF_3CO_2)_2$ to give 84% *ee* value but a lower yield (35%) (Table 2, entry 5). Slow addition of phenylboronic acid (**3a**) to maintain the low concentrations of **3a** might favor the imine addi-

**Table 2.** Optimization of the reaction conditions.[a]

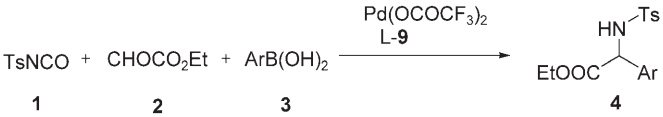



| Entry | Step a | Step b | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | reflux 48 h | $Pd(OAc)_2$ + **L-9** + **3a**, reflux 24 h | 51 | 80 |
| 2 | $AlCl_3$ (10 mol%), reflux 3 h | $Pd(OAc)_2$ + **L-9** + **3a**, reflux 24 h | NR | - |
| 3 | $Pd(CF_3CO_2)_2$, reflux 3 h | **L-9** + **3a**, reflux 24 h | NR | - |
| 4 | $Pd(CF_3CO_2)_2$ + **L-9**, reflux 3 h | **3a**, reflux 24 h | 65 | 76 |
| 5 | $Pd(OAc)_2$ + **L-9**, reflux 3 h | **3a**, reflux 24 h | 35 | 84 |
| 6 | $Pd(CF_3CO_2)_2$ + **L-9**, reflux 3 h | **3a** (slow addition 24 h), reflux 24 h | 77 | 38 |

[a] *Reaction conditions: p*-toluenesulfonyl isocyanate (**1**, 0.355 mmol) with ethyl glyoxylate (**2**, 0.355 mmol), $Pd(OAc)_2$ or $Pd(CF_3CO_2)_2$ (5 mol%), phenylboronic acid (**3a**, 2 equivs.), **L-9** (6 mol%) in refluxing toluene (2 mL), detailed conditions see Table 1.
[b] Isolated yields.
[c] Determined by HPLC analysis using a Chiralcel column.

**Table 3.** Palladium(II)-catalyzed, one-pot enantioselective synthesis of arylglycine derivatives from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate and arylboronic acids.[a]




| Entry | Ar | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | Ph | **4a** | 65 | 75 (+)[d] |
| 2 | 4-$CH_3C_6H_4$ | **4b** | 71 | 70 (+) |
| 3 | 4-$MeOC_6H_4$ | **4c** | 57 | 75 (+) |
| 4 | 4-$ClC_6H_4$ | **4d** | 73 | 81 (+) |
| 5 | 4-$FC_6H_4$ | **4e** | 64 | 64 (+) |
| 6 | 3-$NO_2C_6H_4$ | **4f** | 63 | 68 (+) |
| 7 | 4-$CF_3C_6H_4$ | **4g** | 61 | 71 (+) |
| 8 | 3-$CH_3C_6H_4$ | **4h** | 73 | 70 (+) |
| 9 | β-naphthyl | **4i** | 60 | 72 (+) |
| 10 | α-naphthyl | **4j** | 35 | - |
| 11 | 2-$CH_3C_6H_4$ | **4k** | 23 | - |
| 12 | 2-$ClC_6H_4$ | **4l** | - | - |

[a] *Reaction conditions:* *p*-toluenesulfonyl isocyanate (**1**, 0.355 mmol), ethyl glyoxylate (**2**, 0.355 mmol), $Pd(CF_3CO_2)_2$ (5 mol%), **L-9** (6 mol%) in refluxing toluene (2 mL) for 3 h, then phenylboronic acid (**3a**, 0.71 mmol) was added and reflux comtinued for additional 24 h.

[b] Isolated yields.

[c] Determined by HPLC analysis using a Chiralcel column. The sign of optical rotation is indicated in parentheses.

[d] The absolute configuration of compound **4a** was determined as (*S*) (see Supporting Information).

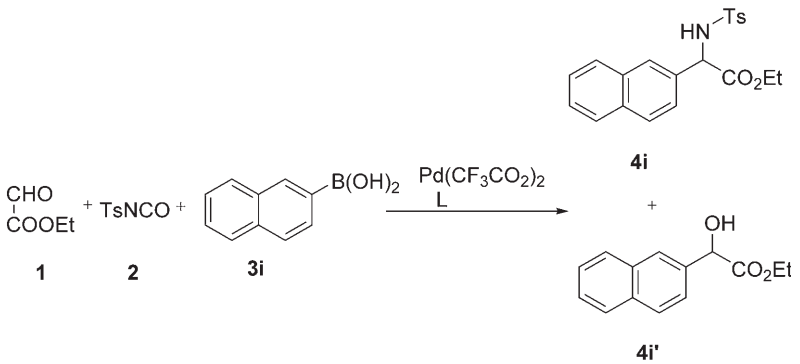
tion to provide higher yields.[13] As expected, the yield was enhanced to 77% but the *ee* value decreased to 38% (Table 2, entry 6).

On the basis of the optimization of the reaction conditions, the scope of this reaction with various aryl-substituted boronic acids was explored. This reaction is tolerant of many functional groups. Arylboronic acids with either electron-neutral groups or electron-donating groups could smoothly add to the imino ester (Table 3, entries 1–3 and 8). To our delight, with arylboronic acids bearing electron-withdrawing groups, which are not efficient for the Petasis reaction[3] and the Jorgensen reaction,[4] this reaction can proceed successfully (Table 3, entries 4–7). The yield from β-naphthylboronic acid was higher than that with α-naphthylboronic acid (Table 3, entries 10 and 11). Sterically hindered *ortho*-substituted arylboronic acids are problematic for our reaction (Table 3, entries 11 and 12).

In the case of using β-naphthylboronic acid as the substrate, a by-product **4i′** (yield: $<5$%) was observed (Scheme 2), which might be formed from the reaction of ethyl glyoxylate (**2**) and β-naphthylboronic acid. However, the amount of **4i′** apparently did not increase when only ethyl glyoxylate (**2**) and β-naphthylboronic acid were reacted under the optimized reaction conditions, implying that the reactivity of ethyl glyoxylate (**2**) is less than that of the the imino ester and our reaction will not be affected.

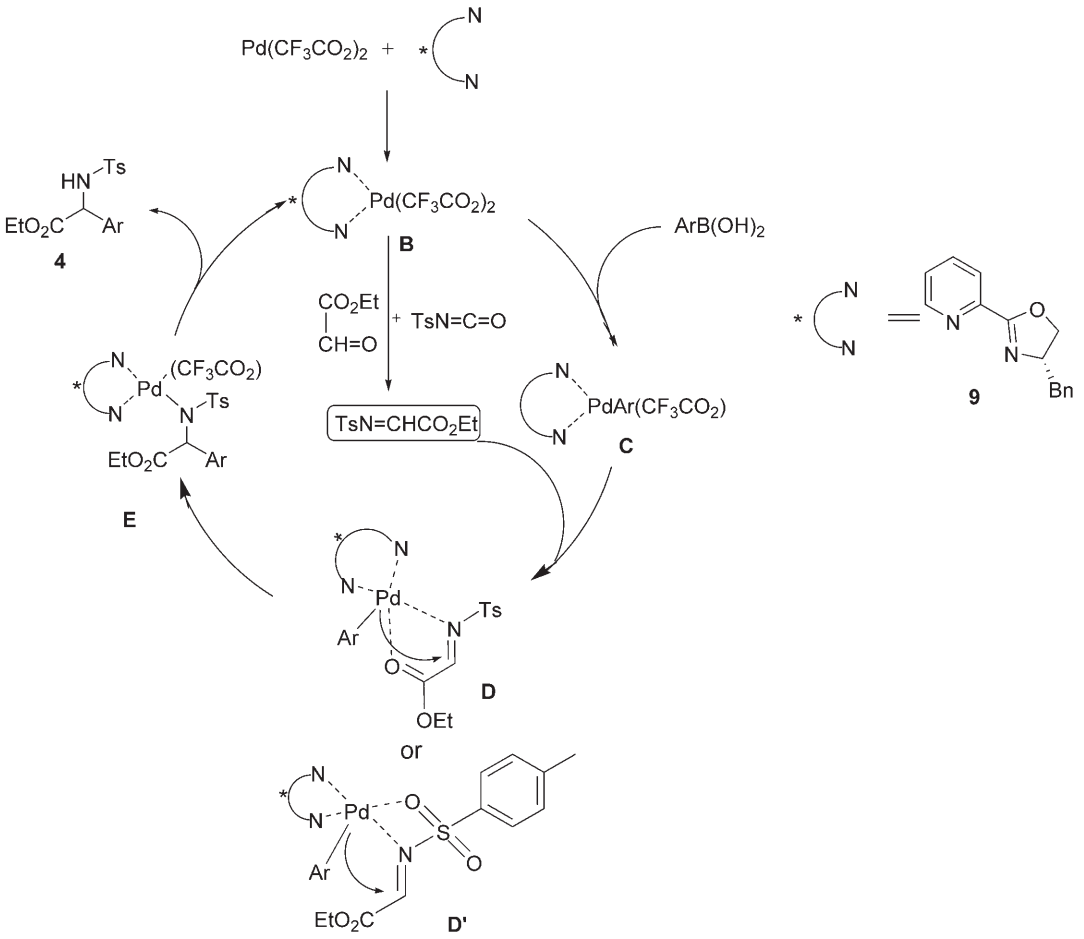
The absolute configuration of product **4a** was determined as (*S*) by comparison with the optical rotation of the sample synthesized from (*S*)-phenylglycine. The removal of the tosyl group from similar amino acids has been reported with no detectable racemization.[3d,f]

The possible mechanism for the addition reaction of arylboronic acids to the imino esters is shown in Scheme 3. First, the combination of $Pd(CF_3CO_2)_2$ and ligand **9** generated the palladium species **B**, which can act as a Lewis acid to catalyze the formation of imino esters. Meanwhile, transmetalation of arylboronic acid with palladium species **B** forms the arylpalladium species **C**, which can be coordinated with imino esters giving intermediate **D** or **D′**.[7,14] The palladium species can activate the imino group due to its Lewis acidity. In addition, both the 1,4-binding mode **D** and the 1,3-binding mode **D′** of the imino esters to palladium make the addition of the aryl group to the imines go in a highly selective manner to produce the addition product **E**, which upon hydrolysis forms product **4** and regenerates the catalytically active species **B** to complete the catalytic cycle.




**Scheme 2.** Formation of a by-product from β-naphthylboronic acid.




**Scheme 3.** Proposed mechanism for the palladium(II)-catalyzed one-pot enantioselective synthesis of arylglycines from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate and arylboronic acids.

In conclusion, a palladium(II)-catalyzed one-pot enantioselective synthesis of arylglycine derivatives from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate and arylboronic acids giving moderate to good yields and enantioselectivity has been developed. In this reaction, the formation of imino esters and the addition of arylboronic acids can be accomplished in one pot, providing a convenient and efficient method for the synthesis of arylglycines.

## Experimental Section

### Typical Procedure

To a Schlenk tube were added *p*-toluenesulfonyl isocyanate (**1**) (0.355 mmol), ethyl glyoxylate (**2**) (0.355 mmol), $Pd(CF_3CO_2)_2$ (5 mol%), and L-**9** (6 mol%) in refluxing toluene (2 mL) for 3 h, then phenylboronic acid (**3a**) (0.71 mmol) was added and reflux continued for another 24 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: EtOAc/petroleum ether) to afford the **4a**; yield: 77 mg (65%).

## Acknowledgements

*This work was supported by the Major State Basic Research Program (2006CB806105). We also thank the National Natural Science Foundation of China (20472099, 20423001, 20332060, 20420130645) and Chinese Academy of Sciences for financial support.*

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