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Diastereoselective Synthesis of Arylglycine Derivatives by Cationic Palladium(II)-Catalyzed Addition of Arylboronic Acids to *N-tert*-Butanesulfinyl Imino Esters

Huixiong Dai and Xiyan Lu*

State Key Laboratory of Organometallic Chemistry, Shanghai, Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

xylu@mail.sioc.ac.cn

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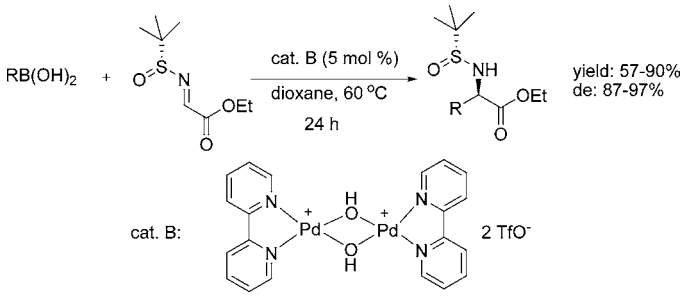
ABSTRACT



A cationic palladium-complex-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinyl iminoacetates to yield the optically active arylglycine derivatives with moderate to good yield and high diastereoselectivity was developed. This reaction provides a convenient and efficient method for the synthesis of arylglycine derivatives.

The insertion of carbon−carbon multiple bonds into carbon transition-metal bonds is an important fundamental reaction in organo transition-metal chemistry.[1] However, direct insertion of the carbon−heteroatom multiple bonds, such as carbonyl, imino, and cyano groups, without using stoichiometric organometallic reagents, has received scant attention.[2] Among the reactions of carbon−heteroatom multiple bonds, the stereoselective addition of organometallic reagents to imines attracts much attention from chemists because it provides a powerful method to afford optically active amines that are important in biological and pharmaceutical fields.[3] However, difficulties arise in the addition of imines because of the poor electrophilicity of the azomethine carbon and the tendency of enolizable imines to undergo deprotonation.[3a] Recently, some progress has been achieved, especially in the catalytic arylation of imines. The most well-known examples are the addition of arylboron reagents to imines mediated by rhodium complexes.[4] In palladium chemistry, only examples of the allylation of imines have been reported.[5] To the best of our knowledge, there is no report concerning the addition of aryl groups to aldimines catalyzed by palladium. The reason may be that the arylpalladium species are more electrophilic[6] and are commonly used in carbon−carbon coupling reactions or in the reactions with alcohols

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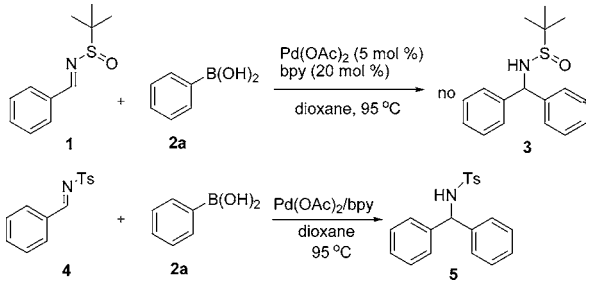
and amines.[1] Thus, it is worth studying the nucleophilic addition of the arylpalladium species to the carbon−heteroatom multiple bonds especially that of aldimines.

As far as we know, the *N*-*tert*-butanesulfinyl group is an excellent auxiliary that not only activates the C═N bond for nucleophilic addition but also exerts a powerful enantioselective induction. In addition, the *N*-*tert*-butanesulfinyl group is easily deprotected,[3a,7] making the *N*-sulfinyl imine a versatile intermediate[8] in the asymmetric synthesis of chiral amines. Herein we report the cationic palladium-complex-catalyzed diastereoselective addition of arylboronic acids to *N*-sulfinyl iminoacetates for the efficient asymmetric synthesis of arylglycine derivatives.

Our group has recently reported the Pd(II)-catalyzed conjugate addition of arylboronic acid to α,β-unsaturated carbonyl compounds[9] and the addition of arylboronic acids to nitriles.[10] We found that the ligand 2,2′-bipyridine (bpy) is crucial in these reactions. The presence of the bpy ligand in these reactions may cause the arylpalladium species to become 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 palladium(II) species.

Initially, we investigated the reaction of (±)-*N*-*tert*-butanesulfinyl imine (**1**) (0.25 mmol) with phenylboronic acid (**2a**) (0.50 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) and bpy (20 mol %) in dioxane (1 mL) at 95 °C; no addition product was formed. While the *N*-tosylbenzaldimine **4** was used as the substrate under the same conditions, the reaction proceeded smoothly, yielding the addition product **5** in 53% yield after 2 days (Scheme 1).

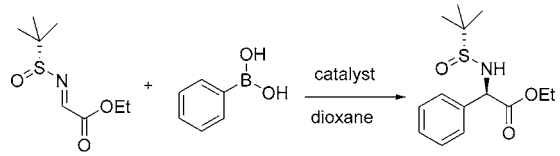
Scheme 1



These results imply that the electrophilicity of *N*-*tert*-butanesulfinyl imine **1** is not sufficient to promote the reaction under our conditions. To improve the electrophilicity and the reactivity of the imine, *N*-*tert*-butanesulfinyl imino esters were chosen as our substrate. The addition of arylboronic acids to imino esters under the catalysis of rhodium has been reported to yield arylglycine derivatives.[4i]

We first investigated the reaction of ethyl ((*R*$_S$)-*N*-*tert*-butanesulfinyl) iminoacetate (**6**) (0.25 mmol) with phenylboronic acid (**2a**) (0.50 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) and bpy (6 mol %) in dioxane (1 mL) at 60 °C; the addition product was obtained in only 17% yield after 24 h (Table 1, entry 1). The low yield showed that a more reactive catalyst system is necessary for this reaction. As compared with the neutral palladium species, such as $Pd(OAc)_2$, the cationic palladium(II) species has vacant coordination sites and shows a harder metal property.[11] Also, in our group's study on the addition of arylboronic acids to nitriles,[10a] the cationic palladium catalyst was found to exhibit higher activity than the neutral palladium species. It occurred to us that the cationic palladium complexes may be useful in catalyzing the addition of arylboronic acids to aldimines.

Table 1. Optimization of Reaction Conditions for the Addition of Phenylboronic Acid (**2a**) to Ethyl ((*R*$_S$)-*N*-*tert*-Butanesulfinyl) Iminoacetate (**6**)[a]



entry	catalyst/L	yield (%)[b]
1	$Pd(OAc)_2$/bpy	17
2	$Pd(CF_3CO_2)_2$/bpy	51
3	cat A	NR
4	cat B	86
5	none	NR

[a] Reaction conditions: phenylboronic acid (**2a**, 0.5 mmol), ethyl ((*R*$_S$)-*N*-*tert*-butanesulfinyl) iminoacetate (**6**, 0.25 mmol), catalyst (5 mol %), L (6 mol %) in dioxane (1 mL) at 60 °C for 24 h. [b] Isolated yields.

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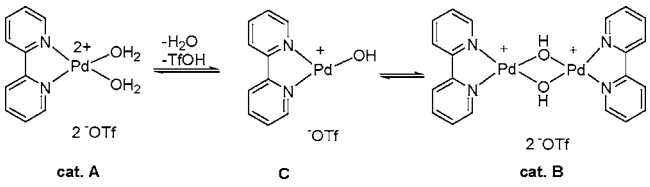
(10) (a) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (b) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765.

(11) Mikami, K.; Hatano, M.; Akiyama, K. *Top. Organomet. Chem.* **2005**, *14*, 279 and references therein.

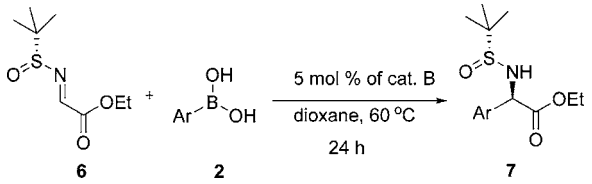
Then, we tried to use cationic $Pd(CF_3CO_2)_2$/bpy as the catalyst system. As expected, the yield increased to 53% (Table 1, entry 2). However, when palladium diaquo catalyst **A** was used as the catalyst, the imines disappeared after 3 h at 60 °C but no addition product was formed (Table 1, entry 3). We next used the binuclear palladium μ-hydroxo catalyst **B** instead of catalyst **A**; to our delight, the yield dramatically increased to 86% with the diastereoselectivity of the arylation product up to 95.5% de (Table 1, entry 4). No addition product was obtained in the absence of the palladium catalyst (Table 1, entry 5). The difference in the reactivity between catalysts **A** and **B** might be due to their difference in equilibrium with the active species **C**. As reported in the literature,[12] 1 equiv of TfOH and H_2O will be generated during the change from catalyst **A** to **C**, while there is no formation of TfOH and H_2O from catalyst **B** to **C** (Scheme 2). The *N*-*tert*-butanesulfinyl group might be cleaved from

Scheme 2



the imino ester by the generated TfOH making the reaction impossible.[8]

Table 2. $[(Bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$-Catalyzed Addition of Arylboronic Acids (**2**) to Ethyl ((R_S)-*N*-*tert*-Butanesulfinyl) Iminoacetate (**6**)[a]



6 **2** **7**

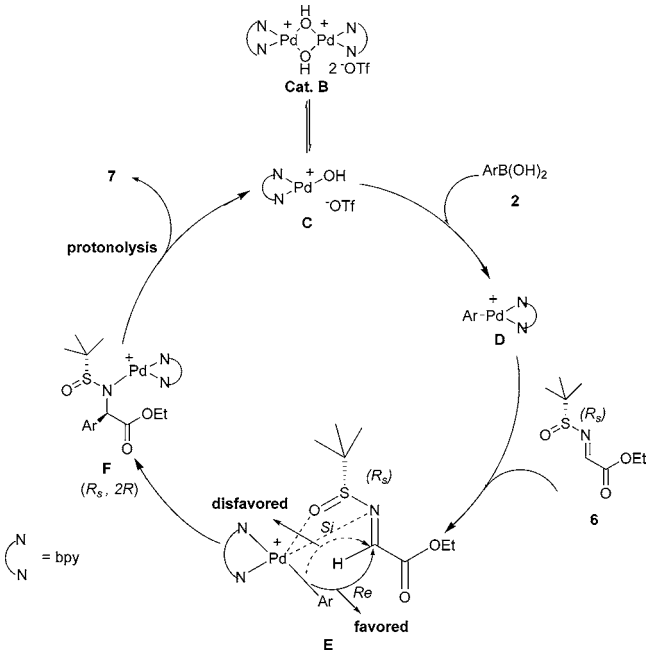
entry	Ar	product	yield (%)[b]	de (%)[c]
1	Ph[d]	**7a**	86	95.5(−)[d]
2	4-$MeOC_6H_4$	**7b**	90	94.8(−)
3	4-$CH_3C_6H_4$	**7c**	65	96.9(−)
4	2-$CH_3C_6H_4$	**7d**	69	93.3(−)
5	3-$CH_3C_6H_4$	**7e**	73	89.4(−)
6	α-naphthyl	**7f**	66	87.3(−)
7	β-naphthyl	**7g**	84	93.7(−)
8	4-$CF_3C_6H_4$	**7h**	57	90.8(−)
9	3-$NO_2C_6H_4$	**7i**	62	88.0(−)
10	4-pyridyl	**7j**	0	

[a] Reaction conditions: $ArB(OH)_2$ (0.50 mmol), ethyl ((R_S)-*N*-*tert*-butanesulfinyl) iminoacetate (**6**, 0.25 mmol), $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (cat **B**, 5 mol %) in dioxane (1 mL) at 60 °C for 24 h. [b] Isolated yields. [c] The diastereoselectivity of the products was determined by measuring the enantiomeric excess of their acetyl derivatives; see Supporting Information. [d] The absolute configuration was determined to be (R_S,2*R*) (see Supporting Information).

The addition of different kinds of arylboronic acids to ethyl ((R_S)-*N*-*tert*-butanesulfinyl) iminoacetate (**6**) was studied as shown in Table 2. This reaction is tolerant of many functional groups. Arylboronic acids with either electron-neutral groups or electron-donating groups could add to the imino esters with moderate to good yields and high diastereoselectivity (Table 2, entries 1−3 and 5), even if the sterically hindered 2-tolyl- and α-naphthylboronic acid also successfully gave the arylglycine products (Table 2, entries 4 and 6). Both the diastereoselectivity and yield were higher for the β-naphthylboronic acid than for the α-naphthylboronic acid (Table 2, entries 6 and 7). Interestingly, electron-withdrawing groups substituted arylboronic acids could also proceed successfully in this reaction with high diastereoselectivity (Table 2, entries 8 and 9). However, no reaction occurred for 4-pyridylboronic acid (Table 2, entry 10). The diastereoselectivity of all products was determined by measuring the enantiomeric excess of their acetyl derivatives, which were obtained by first removing the sulfinyl group and then by acetylation (see Supporting Information).

The possible mechanism for the $[(bpy)Pd^{+}(\mu\text{-}OH)]_2(^{-}OTf)_2$ (catalyst **B**) catalyzed addition reaction of arylboronic acids to the imino esters is proposed as shown in Scheme 3. First, the dimeric catalyst **B** dissociates to the

Scheme 3. Proposed Mechanism for the Addition of Arylboronic Acids to Ethyl ((R_S)-*N*-*tert*-Butanesulfinyl) Iminoacetate (**6**) Catalyzed by Catalyst **B**



active species **C** in the presence of the solvent or the substrate imino ester **6**.[12,13] Due to the high oxophilicity of boron, the coordination of the hydroxyl group of the active species **C**

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with boronic acid facilitates the transmetalation step to form the intermediate **D**.[14] Because of the vacant coordination site on the palladium, both the imino group and the sulfinyl group could coordinate with it[15] very easily to generate intermediate **E**. The imino group can be activated by the cationic palladium species due to its higher Lewis acidity. In addition, because of the 1,3-binding mode of the coordination of the nitrogen atom of the imine and the oxygen atom of the sulfinyl group to the palladium center, the aryl group preferred to add to imines from the *Re* face in a highly selective manner to produce the addition product **F** (R_S,2*R*), which yielded product **7** upon hydrolysis and regenerated the catalytic active intermediate **C**.

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In summary, we have developed a cationic palladium-complex-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl iminoacetates to yield the optically active arylglycine derivatives with moderate to good yield and high diastereoselectivity, which provides a convenient and efficient method for the synthesis of arylglycines. Further studies on probing the detailed mechanism and the transformations of the addition products are currently underway.

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

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