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Catalytic Enantioselective Addition of Arylboronic Acids to *N*-Boc Imines Generated in Situ

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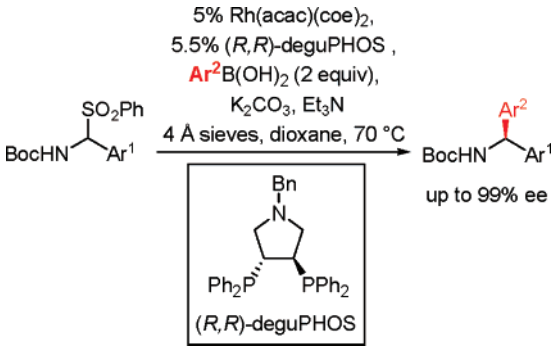
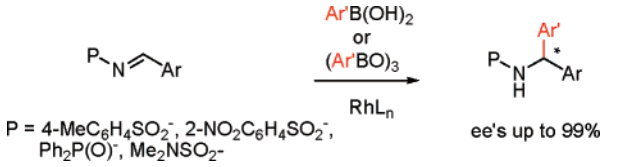
ABSTRACT



The rhodium-catalyzed addition of arylboronic acids to *N*-Boc imines generated in situ from stable and easily prepared α-carbamoyl sulfones has been developed. High enantioselectivities are observed for additions of arylboronic acids with a variety of steric and electronic properties.

Miyaura's first report on the Rh-catalyzed addition of arylboronic acids to activated imines[1] captured the attention of the synthetic organic community due to the preponderance of amines in drugs and due to the synthetic opportunities presented by the large number and diversity of commercially available arylboronic acid inputs. Subsequently, a number of enantioselective variants have been developed that proceed with good yields and very high selectivities (Scheme 1).[2] Most reports describe additions to *N*-toluenesulfonyl imines.[2a,b,f−h] However, due to the harsh conditions necessary to remove the toluenesulfonyl group from the addition product, alternative activating groups have increasingly been investigated, including the 2-nitrobenzenesulfonyl group cleaved by addition of thiolate nucleophiles,[2c] the diphenylphosphinoyl group cleaved with HCl,[2d] and the *N*,*N*-dimethylsulfamoyl group cleaved by refluxing in 1,3-diaminopropane (bp 140 °C) for 2 h.[2e] While these nitrogen protecting groups are more easily cleaved than the toluenesulfonyl group, they either suffer from inconvenient or nonstandard cleavage conditions or, in the case of the diphenylphosphinoyl group, high molecular weight. An additional liability of all of these methods is the inherent hydrolytic lability of activated imines,

Scheme 1. Arylboronic Acid Additions to Activated Imines



(1) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637−1639.

(2) (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128−8129. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584−13585. (c) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307−310. (d) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092−1093. (e) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789−2791. (f) Duan, H. F.; Jia, Y. X.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 2567−2569. (g) Wang, Z. Q.; Feng, C. G.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336−5337. (h) Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett*, **2007**, *14*, 2213−2216.

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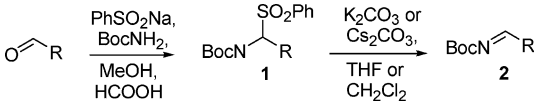
which makes them difficult to manipulate and purify, complicating their use in amine synthesis.[3]

The Boc protecting group is the most extensively used of all amine protecting groups because it is low in molecular weight, is cleaved under convenient acidic conditions (HCl or TFA), and upon deprotection produces volatile byproducts that enable straightforward isolation of pure amine products.[4] Enantioselective catalytic additions to *N*-Boc imines would therefore provide significant practical advantages over additions to other activated imine derivatives.

N-Boc imines **2** show considerable hydrolytic lability (Scheme 2). However, α-carbamoyl sulfones **1**, which serve

Scheme 2. Preparation of *N*-Boc Imines **2**

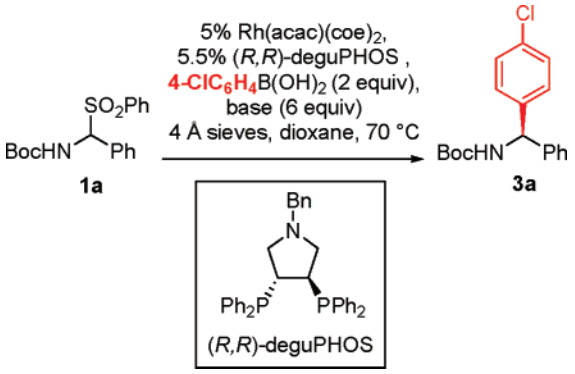


as key intermediates in the most popular route to *N*-Boc imines, are prepared under mild conditions in high yields and are stable, crystalline compounds.[5] We envisioned that in situ generation of imines **2** from the stable α-carbamoyl sulfones **1** during the arylboronic acid addition step would provide a particularly efficient and straightforward protocol (Table 1).[6,7]

We initiated our study on the addition of arylboronic acids to in situ generated *N*-Boc imines by using conditions that we had previously developed for the enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl imines.[2d]

Specifically, $Rh(acac)(coe)_2$ was used as the precatalyst, and deguPHOS[8] was used as the chiral ligand. To minimize imine hydrolysis 4 Å molecular sieves were added, and Et_3N was included because it had been found to result in higher yields. Dioxane was also selected as the solvent because we had previously observed that it gave superior yields and % ee.[2d] Unfortunately, little if any addition product was observed due to inefficient in situ conversion of α-carbamoyl sulfone **1a** to the corresponding *N*-Boc imine **2a** (entry 1, Table 1). A number of anionic bases that might more efficiently convert **1** to **2** were next evaluated. While LiF,

Table 1. Selection of Base for in Situ Generation of *N*-Boc Imine and Enantioselective Arylboronic Acid Addition



entry	base	additive	yield (%)[a]
1	Et_3N	–	<5
2	LiF	–	<5
3	MgO	–	<5
4	NaOMe	–	<5
5	NaOH	–	<50[b]
6	K_2CO_3	–	53
7	Cs_2CO_3	–	51
8	K_2CO_3	Et_3N[c]	76

[a] Isolated yields after chromatography. [b] The addition product was contaminated with inseparable impurities. [c] 1.5 equiv of base was added.

MgO, and NaOMe were not effective (entries 2−4), the relatively strong bases, NaOH (entry 5), K_2CO_3 (entry 6), and Cs_2CO_3 (entry 7) gave promising initial results, with K_2CO_3 and Cs_2CO_3 giving the cleanest conversion to product. Because Et_3N had previously proven to be beneficial in arylboronic acid additions to *N*-diphenylphosphinoyl imines, this additive was evaluated along with K_2CO_3 resulting in a significant increase in yield (entry 8). Notably, chiral HPLC analysis established that the product was obtained with very high selectivity (98% ee). Increasing the reaction time did not increase the yield of the product (data not shown). Presumably, competitive substrate hydrolysis and/or catalyst decomposition prevents complete reaction conversion.

The optimal conditions were next evaluated with a range of different arylboronic acids. Electron-rich arylboronic acids added in good yields and with excellent enantioselectivities (entries 2 and 3, Table 2). Arylboronic acids with electron-withdrawing substituents also added with very high selectivities although with a moderate reduction in yield (entries 4 and 7). The reaction was tolerant of steric interactions with the ortho-methyl-substituted arylboronic acid also adding in reasonable yield and with high selectivity (entry 8).

Additions of arylboronic acids to *N*-Boc imines with diverse structural and electronic properties were next investigated. Additions of phenylboronic acid to *N*-Boc benzaldimines with methyl substitution at the ortho-, meta-, and para-positions each proceeded with high selectivities (entries 9−11). Addition to the ortho-substituted derivative is particularly significant because the increased steric interaction did not appreciably impact reaction yield (entry 11). The

(3) For a comprehensive review on reactivity and properties of activated imines see: Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159−186.

(4) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 518−525.

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(6) To our knowledge, the addition of arylboronic acids to activated imines generated in situ has not previously been reported.

(7) For in situ generation of *N*-Boc imines in an aza-Henry reaction see: Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L. Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975−7978.

(8) DeguPHOS is available from a number of chemical suppliers, including Strem Chemicals, Inc., ACBR GmbH KG, and Degussa AG. Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326−3343.

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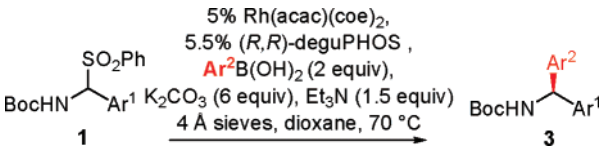
Table 2. Selection of Base for in Situ Generation of *N*-Boc Imine and Enantioselective Arylboronic Acid Addition



entry	Ar^1	Ar^2	yield (%)[a]	ee (%)[b]
1	Ph	4-ClC_6H_4	76	98[c]
2	Ph	4-MeC_6H_4	70	96
3	Ph	4-$MeOC_6H_4$	76	93[c]
4	Ph	4-$CF_3C_6H_4$	51	95[c]
5	Ph	3-ClC_6H_4	55	99
6	Ph	3-MeC_6H_4	66	95
7	Ph	3-AcC_6H_4	52	94
8	Ph	2-MeC_6H_4	62	93
9	4-MeC_6H_4	Ph	71	90
10	3-MeC_6H_4	Ph	70	95
11	2-MeC_6H_4	Ph	63	97
12	4-BrC_6H_4	Ph	59	90
13	2-thienyl	Ph	71	96
14	4-$MeOC_6H_4$	Ph	76	96[c]
15	4-$CF_3C_6H_4$	Ph	69	79[c]

[a] Isolated yields after chromatography. [b] Enantiomeric purity determined by chiral HPLC analysis. [c] Absolute configuration established by comparison of the optical rotation of amine obtained upon Boc cleavage to literature values[9] (see Supporting Information).

addition to *N*-Boc 2-thiophenyl carboxaldimine also proceeded cleanly, demonstrating both compatibility of heterocyclic imines and compounds incorporating sulfur (entry 13). Addition of phenylboronic acid proceeded in good yield and with high enantioselectivity to the electron-rich imine derived from 4-anisaldehyde (entry 14). Interestingly, while clean addition also occurred to the electron-deficient imine derived from 4-trifluoromethylbenzaldehyde, significantly reduced enantioselectivity was observed (entry 15). A final notable feature of this method is the high level of functional group tolerance, with keto (entry 7), alkoxy (entries 3 and 14), bromo (entry 12), and chloro (entry 1 and 5) groups all compatible with the addition reaction.

In conclusion, the enantioselective addition of arylboronic acids to *N*-Boc imines has been reported for the first time. The method was evaluated for a range of functionalized arylboronic acids and *N*-Boc imines, including electron-poor and -rich as well as ortho-substituted derivatives, and very high selectivities were observed for all but one of the substrate combinations examined. The reported method should be of considerable utility due to the well-documented popularity and convenience of *N*-Boc protected amine derivatives. Moreover, this method is considerably more straightforward to carry out than previously reported[2] arylboronic acid additions to imines because the *N*-Boc amine products **3** are obtained in situ from stable and easily prepared α-carbamoyl sulfones **1**.

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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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