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A Room-Temperature Protocol for the Rhodium(I)-Catalyzed Addition of Arylboron Compounds to Sulfinimines

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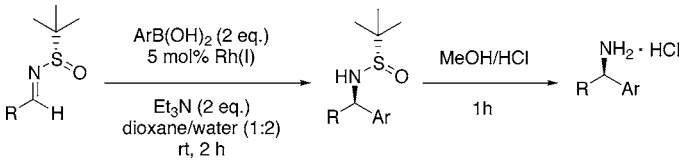
ABSTRACT



The addition of organoboronic acids to chiral sulfinimines proceeds under mild conditions at room temperature, using Rh(I) catalysis in the absence of external phosphine ligands. Clean reaction only occurs in the presence of water as a cosolvent. The sulfinamide adducts are formed with high diastereoselectivities, providing a convenient route to the synthesis of enantiomerically enriched chiral benzylic amines.

Chiral amines are synthetically important targets as a result of their presence in natural products, pharmaceuticals, and other bioactive molecules. For example, chiral benzylic amines such as diarylmethylamines are found in such biologically active compounds as the histamine H1-receptor antagonist (*S*)-cetirizine dihydrochloride[1] and the non-peptide selective opioid receptor agonist SNC80.[2] Although various methods for the enantioselective synthesis of chiral amines are known,[3] a completely general approach to their formation remains elusive. Conceptually one of the most attractive approaches to their synthesis is the enantioselective addition of nucleophilic organometallic species to imine derivatives.[4] The most well-known examples of this strategy are the catalytic asymmetric additions of organzinc reagents (R_2-Zn), including the additions of dialkylzinc reagents (usually diethylzinc or dimethylzinc) to sulfonylimines,[5] *N*-phosphinoylimines,[6] and *N*-arylimines,[7] and the addition of diphenylzinc to in situ generated *N*-formylimines.[8] These additions typically occur in moderate to good ee's, but the protocols employed suffer from several limitations, including the requirement for highly electron-deficient imines, very narrow substrate scope for the organozinc reagents, the use of unusual non-commercial chiral ligands, and the inherent air and water sensitivity of R_2Zn reagents.[9]

A potential solution to at least some of these problems is afforded by the use of metal-catalyzed additions of organoboron compounds.[10] The use of boronic acids rather than other organometallic reagents is highly desirable as a result of their relative stability toward air and moisture, their

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(1) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766−768.

(2) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice K. C. *J. Med. Chem.* **1994**, *37*, 2125−2128.

(3) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Kobayashi, S.; Ishitani H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(4) For a general review on catalyzed asymmetric arylation reactions, see: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308.

(5) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.

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(7) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.

(8) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694.

(9) Dimethylzinc has also been used to promote the addition of alkenylzirconocenes to *N*-phosphinoylimines; see: Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449−2452.

(10) For a review of rhodium-catalyzed asymmetric additions, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844.

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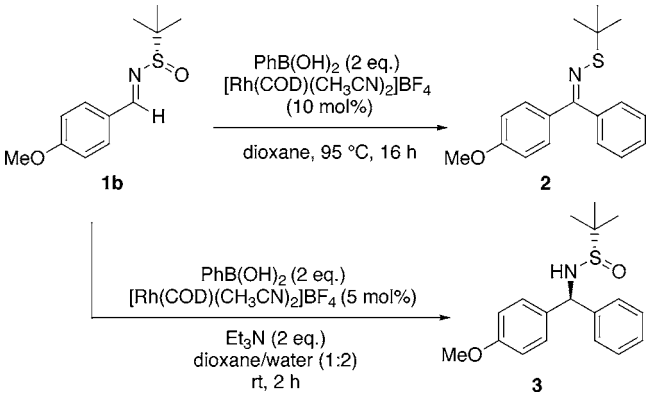
functional group tolerance, and their commercial availability or ease of synthesis. Boronic acids have been shown to undergo addition to imines, as demonstrated by Miyaura's Rh(I)-catalyzed addition of arylboronic acids to sulfonylimines[11,12] and Jamison's Ni(0)-catalyzed three-component coupling of boronic acids, alkynes, and imines.[13] Amidophosphines[14] and C_2-symmetric bicyclo[2.2.2]octadienes[15] have been used as chiral ligands for the addition of triarylboroxines to sulfonylimines at 60−100 °C. The major limitations associated with these protocols are the requirement for triarylboroxines[14,15] rather than arylboronic acids, and in the former case, substrate scope is limited, since high enantioselectivities can be achieved only when reacting *ortho*-substituted sulfonylimines.[14]

Following our earlier studies on the Lewis acid catalyzed addition of crotyl and allyltrifluoroborate salts to *N*-*tert*-butylsulfinimines,[16] our goal at the outset of this project was to develop a convenient room-temperature protocol for the addition of arylboronic acids. Although an auxiliary-based strategy, the use of *N*-sulfinimines is growing in importance due to the ease of introduction and removal of the auxiliaries.[17] The condensation of arylboronic acids and *N*-*tert*-butylsulfinamide with either glyoxylic or pyruvic acid has been reported in a Petasis borono-Mannich reaction but afforded the adducts as 1:1 diastereoisomeric mixtures.[18] While this report appeared to offer little hope for the stereocontrolled addition of an arylboron reagent, a variety of other organometallic reagents (e.g., organo-Li, Mg, Al, and Zn reagents)[17] are known to undergo highly diastereoselective additions to *N*-sulfinimines, including the use of arylmetal reagents.[19] Most significantly, during the course of our studies, Ellman and co-workers disclosed the diastereoselective addition of arylboronic acids to *N*-sulfinimines at 70 °C using catalytic Rh(acac)(coe)$_2$ in the presence of 1,2-bis(diphenylphosphino)benzene.[20] The optimized conditions require heating at 70 °C and slow addition of the boronic acids over 6−10 h. We now demonstrate that diastereoselective addition to *N*-sulfinimines can be achieved using an operationally simpler set of conditions that avoids the use of phosphines, heating, or slow addition of reagents via syringe pump.

Scheme 1. Effect of Water on Rhodium-Catalyzed Addition of Phenylboronic Acid to Sulfinimine **1b**



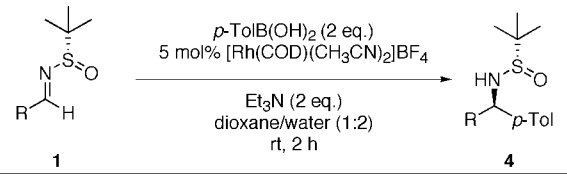
Our investigations have focused upon the use of *N*-*tert*-butanesulfinyl aldimines.[17b,21] Initial attempts at Rh(I)-catalyzed additions under a variety of anhydrous conditions led to the formation of side-products **2** or poor conversions to product **3**. For example, reaction of phenylboronic acid with enantiomerically pure (*S*)-sulfinimine **1b** in the presence of 10 mol % [Rh(COD)(CH$_3$CN)$_2$]BF$_4$ catalyst resulted in no reaction at room temperature but at 95 °C led to the addition-deoxygenation product **2** in 68% yield (Scheme 1). Interestingly, this side-product was not observed in the case of more electron-deficient *N*-*tert*-butanesulfinyl aldimines.

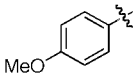
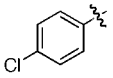
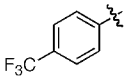
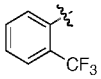
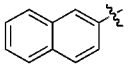
Several other rhodium-based catalysts (e.g., [Rh(COD)Cl]$_2$, Rh(acac)(CO)$_2$, and Rh(acac)(C$_2$H$_4$)$_2$) were submitted to the reaction conditions in the absence of any ligand and in the presence of both monodentate and bidentate phosphine ligands. However, no reaction occurred at room temperature using these catalyst systems. The key breakthrough occurred with the recognition of the importance of triethylamine as an additive and the use of water as a cosolvent. The desired product **3** was obtained in 45% yield and with 82% diastereoselectivity when the solvent system was changed to dioxane and water in a 1:2 ratio, using PhB(OH)$_2$ (2 equiv) and Et$_3$N (2 equiv)[11] at room temperature. The side-product **2** was not formed under these conditions. Reaction under the same conditions but at 95 °C led to **3** in 25% yield and with 79% diastereoselectivity. The best yields were obtained with a heterogeneous 1:2 mixture of dioxane and water. Any attempts to homogenize the system by using equivalent amounts of solvents or adding *tert*-butyl alcohol to the suspension led to lower yields of the compound **3**.

A range of substituted aryl-, heteroaryl-, and alkyl-based *N*-*tert*-butanesulfinimines **1** were reacted with *p*-tolylboronic acid (2 equiv) under a standard set of conditions (Table 1), using 5 mol % of Rh(I) catalyst and Et$_3$N (2 equiv) in

(11) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, *11*, 1637−1639.
(12) For the Rh(I)-catalyzed arylation of *N*-sulfonylimines with arylstannanes using MOP-based ligands at 110 °C, see: Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976−977.
(13) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364−1367.
(14) Kuriyama, M.; Soeta, T.; Hao, X. Y.; Chen, O.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128−8129.
(15) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584−13585.
(16) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382−1383.
(17) For recent reviews, see: (a) Zhou, P.; Chen, B.-C.; Davis F. A. *Tetrahedron* **2004**, *60*, 8003−8030. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.
(18) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865−8868.
(19) For examples of the addition of aryl Grignard and aryllithium reagents to *N*-sulfinylimines, see: (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883−8904. (c) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396−3397. (d) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310. (e) Plum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923−926.
(20) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092−1093.
(21) *N*-*tert*-Butanesulfinyl aldimines are readily synthesized in enantiopure form and in high yields via the condensation of *N*-*tert*-butylsulfinamide and the corresponding aldehydes. See: (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284. (b) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317−1320.

Table 1. Reaction of Sulfinimines **1** with *p*-tolylboronic Acid



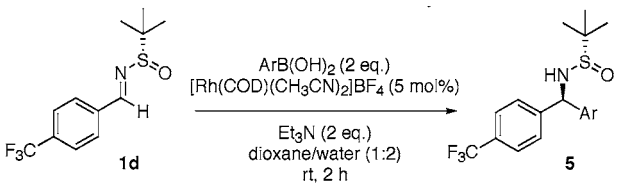
R	Sulfinamide Product	de	Yield[a]
	**4 a**	85%	78%
	**4 b**	≥98%	59%
	**4 c**	83% (91%)[b]	92% (87%)[b]
	**4 d**	91%	quant
	**4 e**	97%	73%
	**4 f**	84% (86%)[c]	80% (92%)[b]
	**4 g**	89%	60%
	**4 h**	97%	58%
	**4 i**	92%	44%

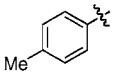
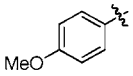
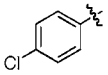
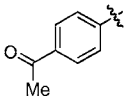
[a] Isolated yields using a standardized set of conditions and reaction times. [b] The reaction was warmed from 0 °C to room temperature over 1 h. [c] 3 equiv of the boronic acid was used.

dioxane/water (1:2) at room temperature for 2 h. The diastereoselectivities of the adducts were generally high (83−98% de). The product yields were more variable, with lower yields being obtained for the alkyl-based products **4i** and **4j** and the nitrile and furan compounds **4e** and **4h**. The effect of the arylboronic acid was probed using the *p*-trifluoromethylphenyl substrate **1d** under the standard set of conditions (Table 2). Good stereoselectivities were obtained for a range of arylboronic acids, including both electron-rich and electron-poor examples. However, the reaction yields were sensitive to steric and electronic effects on the boronic acid (**5d** and **5e**, Table 2).

The reaction conditions outlined in this paper differ considerably from those employed by Ellman, and it is appropriate to comment on the differences. The importance of water under our conditions is consistent with a mechanism in which the arylboronic acid $Ar^1B(OH)_2$ undergoes transmetalation with the catalyst to an Ar^1-Rh(I) species. This then undergoes insertion (addition) with **1** to produce an $(Ar^1R^2HC)(SO\textit{t}Bu)N$-Rh(I) intermediate. In the presence of water, hydrolysis of this species would give the product (e.g., **3**) and regenerate the active Rh(I)-OH species required for transmetalation.[22] In the absence of water, either β-hydride elimination or deoxygenation/proton loss would give **2**. We

Table 2. Reactions of **1d** with Different Arylboronic Acids



$ArB(OH)_2$	Sulfinamide Product	de	Yield[a]
	**5 a**	93%	94%
	**4 d**	91%	quant
	**5 b**	89%	84%
	**5 c**	92%	83%
	**5 d**	93%	47%
	**5 e**	83%	67%

[a] Isolated yields using a standardized set of conditions and reaction times.

believe that the use of triethylamine may serve as a buffer to prevent protonation of the intermediate Ar^1-Rh(I) species, which occurs under acidic conditions.[23] Indeed, Ellman suggests that slow-addition of the arylboronic acids by syringe-pump is required to prevent arylboronic acid-catalyzed protonation.[20] Finally, we believe the choice of a cationic Rh(I) catalyst precursor, using the conditions described herein, may lead to a more active catalyst system, either due to enhanced transmetalation ability by the Rh(I)-OH species or due to the greater reactivity of the Ar^1-Rh(I) species in the addition step.

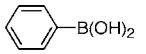
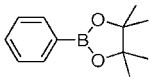
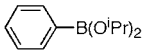
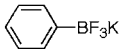
The major diastereoisomers of the adducts obtained in these additions are consistent with addition of the aryl-rhodium species to **1** via a nonchelated transition state, as has been proposed for the addition of organolithium reagents.[17,19] The chiral auxiliary of the sulfinamide products **4**/**5** is readily removed under acidic methanolysis conditions at room temperature. For example, sulfinamides **5a**, **4f**, and **4h** were deprotected in 76%, 86%, and 70% yields, respectively, to afford the amines as their HCl salts **6**, with no detectable loss of enantiopurity.

In addition to boronic acids, other boronic acid equivalents also undergo reaction (Table 3). Under the standard conditions, phenylpinacol boronate ester, phenylisopropyl boronate

(22) A similar mechanism has been demonstrated for the case of Rh(I)-catalyzed addition of phenylboronic acids to enones; see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *126*, 5052−5058.

(23) (a) Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179−184. (b) Boyd, S. E.; Field, L. D.; Hambley, T. W.; Partridge, M. G., *Organometallics* **1993**, *12*, 1720−1724.

Table 3. Reactions of **1d** with Different Phenylboron Derivatives to Form **5a**

Arylboron Derivative	de	Yield[a]
	93%	94%
	95%	79%
	88%	65%
	92%	61%

[a] Isolated yields using a standardized set of conditions and reaction times.

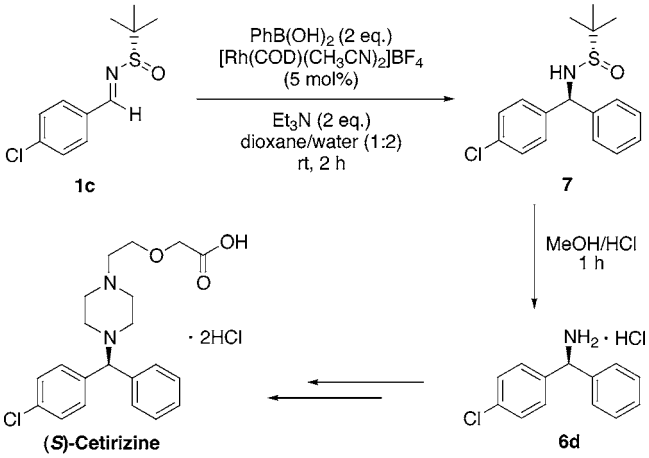
ester and phenyl potassium trifluoroborate salt all reacted with **1d** to give **4d** in diastereoselectivities comparable to that of phenylboronic acid.

This Rh(I)-catalyzed method was applied in a formal synthesis of **6d**, which is useful as a precursor for (*S*)-cetirizine (Scheme 2).[19e,24] Sulfinimine **1c** was reacted with phenylboronic acid in the presence of the Rh(I) catalyst to afford **7** in 83% yield and 90% de. The chiral auxiliary was then cleaved under acidic conditions to give product **6d** in 95% yield and 90% de.

In conclusion, rhodium-catalyzed diastereoselective additions of arylboron compounds to *N*-sulfinylimines have been demonstrated. The sufinamide adducts are obtained with high diastereoselectivities and provide ready access to enantiomerically enriched diarylmethylamines. The reactions proceed under milder conditions than those recently outlined by Ellman and co-workers, occurring over 2 h at room temperature, without the need for the addition of an external phosphine ligand or syringe pump addition of the arylboronic acids. This feature may prove advantageous, as for example in parallel synthesis applications.

(24) The racemic version of cetirizine is a histamine H1-receptor antagonist, and is used to treat the symptoms of allergic rhinitis. (*R*)-Cetirizine (levocetirizine) is known to bind with twice the affinity of racemic cetirizine to the human H1-receptor; see: Gillard, M.; Van Der Perren, C.; Moguilevsky, N.; Massingham, R.; Chatelain, P. *Mol. Pharmacol.* **2002**, *61*, 391−399.

Scheme 2. Formal Synthesis of (*S*)-Cetirizine



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

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