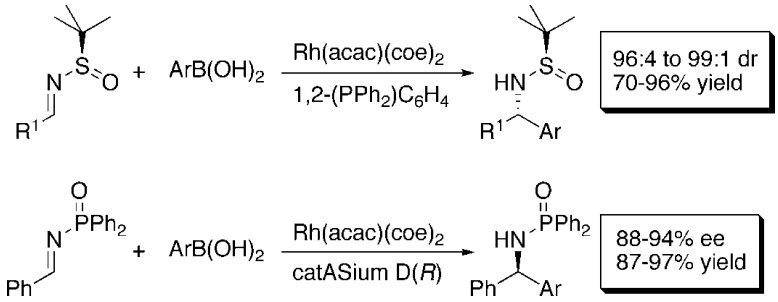
Communication

# Diastereoselective and Enantioselective Rh(I)-Catalyzed Additions of Arylboronic Acids to *N*-*tert*-Butanesulfinyl and *N*-Diphenylphosphinoyl Aldimines

Daniel J. Weix, Yili Shi, and Jonathan A. Ellman

*J. Am. Chem. Soc.*, **2005**, 127 (4), 1092-1093• DOI: 10.1021/ja044003d • Publication Date (Web): 07 January 2005






## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 25 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 01/07/2005

# Diastereoselective and Enantioselective Rh(I)-Catalyzed Additions of Arylboronic Acids to *N-tert*-Butanesulfinyl and *N*-Diphenylphosphinoyl Aldimines

Daniel J. Weix, Yili Shi, and Jonathan A. Ellman*

*Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720*

Received October 1, 2004; E-mail: jellman@uclink.berkeley.edu

Chiral, α-branched amines are prevalent, essential components of many drugs and drug candidates, and therefore, general methods for their asymmetric synthesis are of considerable importance. The stereoselective addition of organometallic reagents to imines represents one of the most convergent and efficient approaches,[1] and the diastereoselective addition of Grignard and lithium reagents to *N-tert*-butanesulfinyl imines has proven to be a particularly reliable and popular method.[2] However, despite recent advances in the synthesis of functionalized Grignard and organolithium reagents,[3] a more functional group tolerant method remains highly desirable.

Arylboronic acids are extremely useful organometallic reagents because they are stable compounds that can easily be prepared displaying a wide array of functionality, and large numbers are commercially available. Although arylboronic acids are poor nucleophiles, rhodium(I) phosphine complexes have been found to efficiently catalyze their addition to *N*-arenesulfonyl imines.[4,5] Recently, good to excellent enantioselectivities have been reported with chiral ligands.[4b,c] However, these methods are limited to aryl aldimines, and the *p*-toluenesulfonyl-protecting group could only be cleaved using a large excess of the costly, high molecular weight reagent, $SmI_2$. The cleavage conditions led to significant hydrodehalogenation of the 4-chlorobenzhydrylamine product.

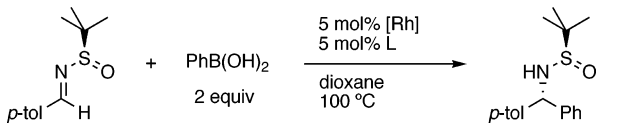
We report here the highly diastereoselective addition of arylboronic acids to both *aromatic and aliphatic N-tert*-butanesulfinyl imines as well as the initial disclosure of the highly enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl benzaldimine. Importantly, both the *N-tert*-butanesulfinyl group and the *N*-diphenylphosphinoyl group can be cleaved under mildly acidic conditions that tolerate even sensitive functionality.[2,6]

While various cationic rhodium complexes catalyzed the addition of phenylboronic acid (PBA) to *N*-sulfinyl imine **1a** with promising levels of diastereoselectivity (Table 1, entries 1−3), the initial low conversions could not be improved upon.[7] In contrast, Rh(acac)-$(coe)_2$-catalyzed reactions were accelerated by the presence of bisphosphines with a two-carbon backbone and gave high diastereoselectivities (entries 4−9). 1,2-Bis(diphenylphosphino)benzene (dppbenz) formed the most active catalyst by a large margin (entry 9).

The reaction concentration was varied to further improve the yield, but higher concentrations resulted in lower conversions (Table 1, entries 10 and 11), while a lower concentration gave a modest increase in conversion (entry 12). Moreover, increasing the number of equivalents of PBA also did not improve the yield (entry 13). By following the reaction by $^1$H NMR, we observed that benzene formation was competitive with imine addition, perhaps explaining the effects of concentration and boronic acid stoichiometry. Rh(I)-phenyl species can be decomposed by acids via a protonation and reductive elimination mechanism that generates benzene.[8] If this is the operative mechanism for the side reaction that produces benzene, with PBA serving as the acid, then the rate of benzene formation should be dependent on [PBA]$^2$ while the desired imine addition should only be dependent upon [PBA]. Slow addition of PBA should maintain low concentrations of PBA and, therefore, should favor imine addition to provide significantly higher product yields.

We were gratified to find that when PBA in dioxane was added over 6 h, addition product **2a** was obtained in 96% yield with high diastereoselectivity (Table 2, entry 1). Notably, the method provides the first rhodium(I)-catalyzed addition of arylboronic acids to aliphatic imines (entries 2−5). The successful addition of 3-acetylphe-

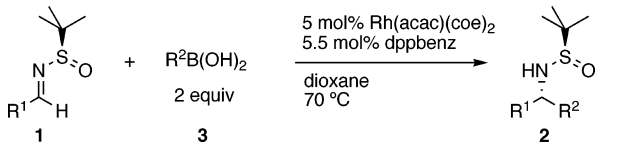
***Table 1.*** Catalyst Optimization




| No. | [Rh] | L | conv. (%)[a] | dr |
|---|---|---|---|---|
| 1[b] | $[Rh(cod)(MeCN)_2]BF_4$ | − | 25[c] | 91:9 |
| 2 | $[Rh(cod)(MeCN)_2]SbF_6$ | − | 5 | 93:7 |
| 3 | $[Rh(cod)_2]SbF_6$ | − | 11 | 92:8 |
| 4 | $Rh(acac)(coe)_2$ | dppm | 11 | 92:8 |
| 5 | $Rh(acac)(coe)_2$ | dppe | 42 | 96:4 |
| 6 | $Rh(acac)(coe)_2$ | dppp | 18 | 98:2 |
| 7 | $Rh(acac)(coe)_2$ | dppb | 7 | 96:4 |
| 8 | $Rh(acac)(coe)_2$ | dppf | 2 | 96:4 |
| 9 | $Rh(acac)(coe)_2$ | dppbenz | 65 | 96:4 |
| 10[d] | $Rh(acac)(coe)_2$ | dppbenz | 58 | 97:3 |
| 11[e] | $Rh(acac)(coe)_2$ | dppbenz | 45 | 96:4 |
| 12[f] | $Rh(acac)(coe)_2$ | dppbenz | 69 | 96:4 |
| 13[g] | $Rh(acac)(coe)_2$ | dppbenz | 65 | 97:3 |

[a] Conversion and dr determined by HPLC. [b] Reaction performed with 3 mol % rhodium. [c] Isolated yield after chromatography. [d] Reaction run at 0.5 M in imine. [e] Reaction run at 1.0 M in imine. [f] Reaction run at 0.13 M in imine. [g] Reaction run with 5 equiv of phenylboronic acid.

***Table 2.*** Substrate Scope




| No.[a] | $R^1$ | $R^2$ | yield (%)[b] | dr |
|---|---|---|---|---|
| 1 | 4-methylphenyl | phenyl (**3a**) | 96 | 97:3 |
| 2 | 2-phenylethyl | phenyl (**3a**) | 86 | 96:4 |
| 3 | 2-phenylethyl | 4-methoxyphenyl (**3b**) | 70 | 96:4 |
| 4 | 2-phenylethyl | 4-($CF_3$)phenyl (**3c**) | 73 | 96:4 |
| 5 | 2-phenylethyl | 3-acetylphenyl (**3d**) | 80 | 98:2 |
| 6 | phenyl | 4-methoxyphenyl (**3b**) | 76 | 98:2 |
| 7 | phenyl | 4-($CF_3$)phenyl (**3c**) | 71 | 98:2 |
| 8 | phenyl | 4-chlorophenyl (**3e**) | 93 | 99:1 |

[a] See Supporting Information for reaction details, dr determination, and assignment of configuration. [b] Isolated yields after chromatography.



10.1021/ja044003d CCC: $30.25 

***Scheme 1.*** One-Pot Conversion of Aldehydes to Amines

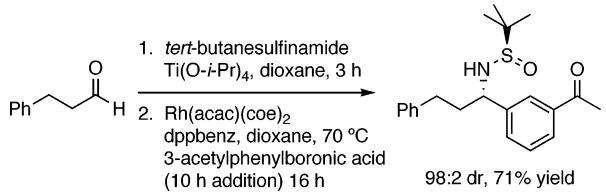
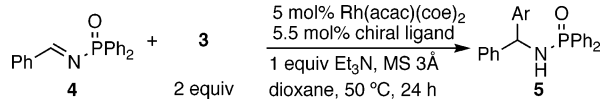



***Table 3.*** Catalytic Enantioselective Reaction




| No.[a] | chiral ligand | 3 | yield (%)[b] | ee (%) | configuration |
|---|---|---|---|---|---|
| 1[c] | dppbenz | **3e** | 99 | − | ± |
| 2[c] | (*R*)-tol-BINAP | **3e** | 89 | 32 | R |
| 3 | (*R*)-PROPHOS | **3e** | 35 | 65 | R |
| 4[c] | (*R*,*R*)-*i*-Pr-DUPHOS | **3e** | 86 | 60 | R |
| 5 | (*S*,*S*)-NORPHOS | **3e** | 37 | 75 | S |
| 6 | (*R*,*R*)-Et-BPE | **3e** | 45 | 90 | S |
| 7 | (*R*,*R*)-DeguPHOS | **3e** | 46 | 96 | R |
| 8[c] | (*R*,*R*)-DeguPHOS | **3e** | 97 | 94 | R |
| 9[c,d] | (*R*,*R*)-DeguPHOS | **3d** | 93 | 88 | R[e] |
| 10[c,d] | (*R*,*R*)-DeguPHOS | **3c** | 87 | 88 | R[e] |
| 11[c,d] | (*R*,*R*)-DeguPHOS | **3b** | 93 | 93 | R[e] |

[a] See Supporting Information for reaction details, ee determination, and assignment of configuration. [b] Isolated yields after chromatography. [c] Reactions were run at 70 °C. [d] Reaction run with 3 equiv of **3** added over 20 h.[13] [e] Configuration assigned by analogy.

nylboronic acid demonstrates the promising functional group tolerance of the reaction (entry 5).[5] Moreover, both arylboronic acids with electron-donating (entries 3 and 6) and -withdrawing (entries 4, 7, and 8) substituents add effectively.

To enhance the efficiency of the method, a one-pot procedure for the asymmetric synthesis of **2** from the starting aldehyde was developed. Condensation of hydrocinnamaldehyde with *tert*-butanesulfinamide in the presence of Ti(*i*-Pr-O)$_4$ in dioxane, followed by addition of catalyst and then slow addition of **3d**, directly provided **2** ($R^1$ = 2-phenylethyl, $R^2$ = 3-acetylphenyl) with high diastereoselectivity and in 71% yield (Scheme 1).

We concurrently pursued the catalytic enantioselective addition of arylboronic acids to achiral imines. The diphenylphosphinoyl group is one of the most desirable of the available achiral imine activating groups because it is easily cleaved from the addition products.[1b,6] When the optimal conditions for additions to *tert*-butanesulfinyl imines were applied to diphenylphosphinoyl imine **4**, only imine hydrolysis was observed. However, when the reaction was performed in the presence of activated, powdered MS 3 Å and 1 equiv of $Et_3N$, a quantitative yield of racemic product **5** could be obtained (Table 3, entry 1).[9,10] A screen of a wide variety of chiral bisphosphines revealed that acceptable conversions were only observed for bisphosphines with a two-atom backbone or a binaphthyl backbone, which is consistent with the additions to *N*-*tert*-butanesulfinyl imines.[11] Most importantly, the bisphosphine (+)-(3*R*,4*R*)-bis(diphenylphosphino)-1-benzylpyrrolidine ((*R*,*R*)-DeguPHOS)[12] provided **5** in near quantitative yield and with very high enantioselectivity (entry 8). The addition of electron-rich and -poor as well as functionalized arylboronic acids also proceeded with good yields and selectivities (entries 9−11). The diphenylphosphinoyl group was also easily cleaved using HCl/MeOH to afford the pure amine hydrochloride in 95% yield with little to no loss in stereochemical purity.[7]

In summary, two new, highly practical methods for the asymmetric synthesis of α-branched amines have been developed. The addition of arylboronic acids to both aliphatic and aromatic *N*-sulfinyl imines proceeds with very high dr, and imine synthesis and arylboronic acid addition can be accomplished in one pot. The enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl imine **4** also proceeded with high enantioselectivity and yield. Further determination of the scope and generality of these methods is ongoing.

**Acknowledgment.** This work was supported by the NSF CHE0446173. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a sponsoring member and Novartis as a supporting member.

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

## References

(1) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405−5511. (c) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694. (d) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247. (e) Li, S.-W.; Batey, R. *Chem. Commun.* **2004**, 1382−1383.

(2) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923−926. (c) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310. (d) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195−4197. (e) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215−4218. (f) Cooper, I. R.; Grigg, R.; Hardie, M. J.; MacLachlan, W. S.; Sridharan, V.; Thomas, W. A. *Tetrahedron Lett.* **2003**, *44*, 2283−2285. (g) Rech, J. R.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495−1498. (h) Jung, P. M.; Beaudegnies, R.; De Mesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293−297. (i) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983−986. (j) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock M. G. *Tetrahedron Lett.* **2004**, *45*, 6641−6643. (k) Jayathilaka, L. P.; Deb, M.; Standaert, R. F. *Org. Lett.* **2004**, *6*, 3659−3662.

(3) For functionalized Grignard reagents, see: (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320. For functionalized lithium reagents, see: (b) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867−926.

(4) (a) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637−1639. (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, 8128−8129. (c) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584−13585.

(5) Rhodium-catalyzed additions of arylboronic acids to aldehydes and α,β-unsaturated ketones proceed with a high level of functional group compatibility. (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196.

(6) (a) Ramage, R.; Hopton, D.; Parrott, M.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357−1370. (b) Osborn, H. M. I.; Sweeney, J. B. *Synlett* **1994**, 145−147. (c) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364−7375.

(7) See Supporting Information for details and complete tables of results.

(8) (a) Kiem, 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.

(9) Under these conditions, the arylboronic acid may form boroxime−$Et_3N$ complexes, which may transmetalate more rapidly. See: McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 5088−5090.

(10) In contrast, MS 3 Å/$Et_3N$ did not improve the conversion for addition of arylboronic acid **3b** to *N*-sulfinyl imine **1** ($R^1$ = 2-phenylethyl).

(11) Other ligands screened gave very low conversions; for example, PHANEPHOS, DIOP, QUINAP, JOSIPHOS, WALPHOS, MANDYPHOS, *i*-Pr-PHOX, Me-BPE.

(12) This ligand is available as "catASium D(*R*)" from Strem Chemicals, Inc. and ACBR, GmbH. Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326−2243.

(13) Quantities of 3.6 (ref 4c) to 5.0 (ref 4b) equiv of arylboronic acid are generally used with *N*-toluenesulfonyl imine substrates in similar reactions.

JA044003D