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Highly Functional Group Compatible Rh-Catalyzed Addition of Arylboroxines to Activated *N-tert*-Butanesulfinyl Ketimines

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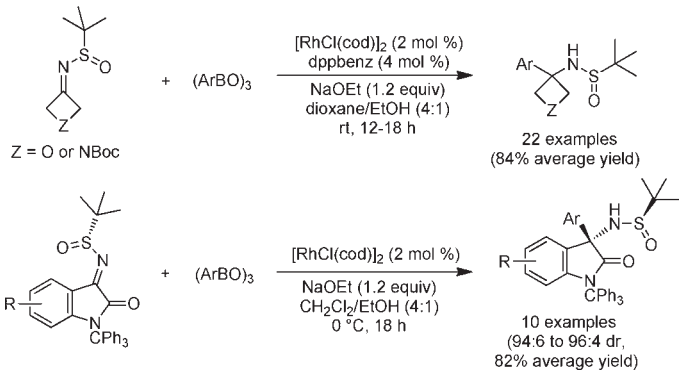
ABSTRACT



The rhodium-catalyzed addition of readily accessible arylboroxines to *N-tert*-butanesulfinyl ketimines derived from oxetan-3-one, *N*-Boc-azetidin-3-one, and isatins proceeds in high yields with excellent functional group compatibility. Moreover, high diastereoselectivities are observed for the additions to the *N*-sulfinyl ketimines derived from isatins.

The addition of nucleophiles to *N-tert*-butanesulfinyl imines is one of the most extensively used approaches for the asymmetric synthesis of amines[1] and, increasingly, for the synthesis of achiral amine products such as tertiary carbinamines.[2,3] *N-tert*-Butanesulfinyl imines show good stability to hydrolysis and tautomerization and can readily be prepared in a single step typically in high yields from carbonyl compounds with diverse steric and electronic properties. The low molecular weight and ease of removal of the *tert*-butanesulfinyl amine protecting group further contribute to the utility of this chemistry. The synthesis of amines by the Rh-catalyzed addition of organoboron reagents to *N-tert*-butanesulfinyl imines is particularly useful due to both high functional group compatibility and the very large number of commercially available, air stable arylboronic acid reagents. The asymmetric synthesis of a broad range of amines using this approach has been achieved by the Rh-catalyzed addition of aryl[4] and alkenyl[5] boron reagents to *N-tert*-butanesulfinyl aldimines, including aryl and alkyl aldimines,[4a,b] glyoxylate-

(1) For reviews on *tert*-butanesulfinyl imine chemistry, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.

(2) For the straightforward recycling of the *tert*-butanesulfinyl group in applications of racemic *tert*-butanesulfinamide, see: Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646.

(3) For select applications of racemic sulfinamide in tertiary carbinamine synthesis, see: (a) Caldwell, J. J.; Collins, I. *Synlett* **2006**, 2565. (b) Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5435. (c) Shao, P. P.; Ye, F.; Weber, A. E.; Li, X.; Lyons, K. A.; Parsons, W. H.; Garcia, M. L.; Priest, B. T.; Smith, M. M.; Felix, J. P.; Williams, B. S.; Kaczorowski, G. J.; McGowan, E. M.; Abbadie, C.; Martin, W. J.; McMasters, D. R.; Gao, Y.-D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5334. (d) Sealy, J. M.; Truong, A. P.; Tso, L.; Probst, G. D.; Aquino, J.; Homa, R. K.; Jagodzinska, B. M.; Dressen, D.; Wonea, D. W. G.; Brogley, L.; John, V.; Tung, J. S.; Pleiss, M. A.; Tucker, J. A.; Konradi, A. W.; Dappen, M. S.; Toth, G.; Pan, H.; Ruslim, L.; Miller, J.; Bova, M. P.; Sinha, S.; Quinn, K. P.; Sauer, J.-M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6386. (e) Shiau, T. P.; Houchin, A.; Nair, S.; Xu, P.; Low, E.; Najafi, R.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1110. (f) Low, E.; Nair, S.; Shiau, T.; Belisle, B.; Debabov, D.; Celeri, C.; Zuck, M.; Najafi, R.; Georgopapadakou, N.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 196.(g) Hamzik, P. J.; Brubaker, J. D. *Org. Lett.* **2010**, *12*, 1116.

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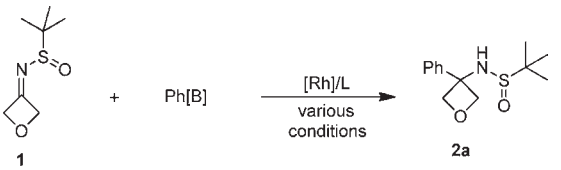
Table 1. Optimization of Reaction Conditions[a]



entry	[Rh] catalyst	ligand	Ph[B] (equiv)	additive (equiv)	solvent	temp (°C)	yield[b] (%)
1	$[Rh(acac)(coe)_2]$	dppbenz	$PhB(OH)_2$ (2.0)	Et_3N (2.0)	dioxane	70	37[c]
2	$[Rh(MeCN)_2(cod)]BF_4$	–	$PhB(OH)_2$ (2.0)	Et_3N (2.0)	1:2 dioxane/H_2O	rt	10[d]
3	$[RhOH(cod)]_2$	dppbenz	$PhBF_3K$ (2.0)	Et_3N (2.0)	2:3 DMF/H_2O	60	0[d]
4	$[RhCl(cod)]_2$	^{S}SPhos	$PhB(OH)_2$ (2.0)	NaOH (1.2)	H_2O	80	0[d]
5	$[RhCl(cod)]_2$	^{S}SPhos	$PhB(OH)_2$ (2.0)	NaOEt (1.2)	EtOH	rt	29[e]
6	$[RhCl(cod)]_2$	^{S}SPhos	$(PhBO)_3$ (1.5)	NaOEt (1.2)	EtOH	rt	70[e]
7	$[RhCl(cod)]_2$	–	$(PhBO)_3$ (1.5)	NaOEt (1.2)	EtOH	rt	71[e]
8	$[RhCl(cod)]_2$	–	$(PhBO)_3$ (1.5)	NaOEt (1.2)	4:1 dioxane/EtOH	rt	84[f]
9	$[RhCl(cod)]_2$	–	$(PhBO)_3$ (1.5)	NaOEt (1.2)	dioxane	rt	0
10	$[RhCl(cod)]_2$	dppbenz	$(PhBO)_3$ (1.5)	NaOEt (1.2)	4:1 dioxane/EtOH	rt	quant

[a] General reaction conditions: 4 mol % of rhodium and 4 mol % of ligand were used. The reaction time was 18 h. [b] Yields were determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an external standard. [c] 9% of imine **1** remained. [d] Imine **1** was completely consumed. [e] Ethoxy addition byproduct was observed in 20−30% yield. [f] Ethoxy addition product was observed in < 5% yield.

derived aldimines,[4c] and trifluoroacetaldimines.[4d] However, to date the Rh-catalyzed addition of organoboron reagents to *N*-sulfinyl ketimines has not been reported.[6] We report here the highly functional group compatible Rh-catalyzed addition of readily available arylboroxines to activated *N*-*tert*-butanesulfinyl ketimines to provide 3-aminooxetanes,[7,8] 3-aminoazetidines,[9] and 3-aminooxindole[10] tertiary carbinamines. Notably, each of these pharmacophores has seen recent and extensive use in drug candidates.[7,10]

We began our investigation by exploring a variety of reaction conditions for phenyl boron reagent addition to imine **1**, which is activated by both ring strain and the electronegative ring oxygen (Table 1). Under our previously developed reaction conditions for additions to *N*-sulfinyl aldimines,[4a] a 37% yield of the desired product **2a** was obtained (entry 1). Reported aqueous reaction conditions[4b,5,11] for organoboron reagent addition resulted in complete consumption of imine **1**, but little if any desired product was observed (entries 2−4). However, when the base and solvent were changed to NaOEt and EtOH, respectively, a 29% yield of **2a** was obtained even at room temperature (entry 5). Because hydrolysis of **1** was problematic, in order to exclude water, we next evaluated arylboroxines, which are conveniently obtained by drying commercially available arylboronic acids. Indeed, when phenylboroxine was used, a considerable increase in product yield was observed (entry 6). Significantly, the catalyst in the absence of the sulfonated S-Phos ligand had identical reactivity (entry 7), suggesting that this bulky monodentate ligand was not participating in the active catalyst. When EtOH was used as the sole solvent an ethoxy-addition byproduct was formed in 20−30% yield (entries 5−7). This side reaction was minimized by using 20% EtOH in dioxane (entry 8). In contrast, no reaction occurred in the absence of EtOH (entry 9). Notably, addition of 1,2-bis(diphenylphosphino)benzene (dppbenz) to air stable $[RhCl(cod)]_2$ provided the product in quantitative yield (entry 10).

To establish the reaction scope, a variety of arylboroxines was explored (Scheme 1). Electron-rich arylboroxines with *para*- and *meta*-substituents were well tolerated (**2b**−**2e**). However, the *ortho*-methylphenylboroxine resulted in a poor conversion even at 60 °C (**2f**), presumably due to

(4) (a) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481. (c) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (d) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633.

(5) (a) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850. (b) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147.

(6) Hayashi and co-workers have recently published on the first example of Rh-catalyzed additions of organoboron reagents to ketimines with the enantioselective catalytic addition of sodium tetraarylborates and potassium aryltrifluoroborates to *N*-sulfonyl aromatic ketimines using chiral diene ligands. (a) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (b) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977.

(7) For recent reviews on the high level of utility of oxetanes in drug discovery, including 3-amino derivatives, see: (a) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052.

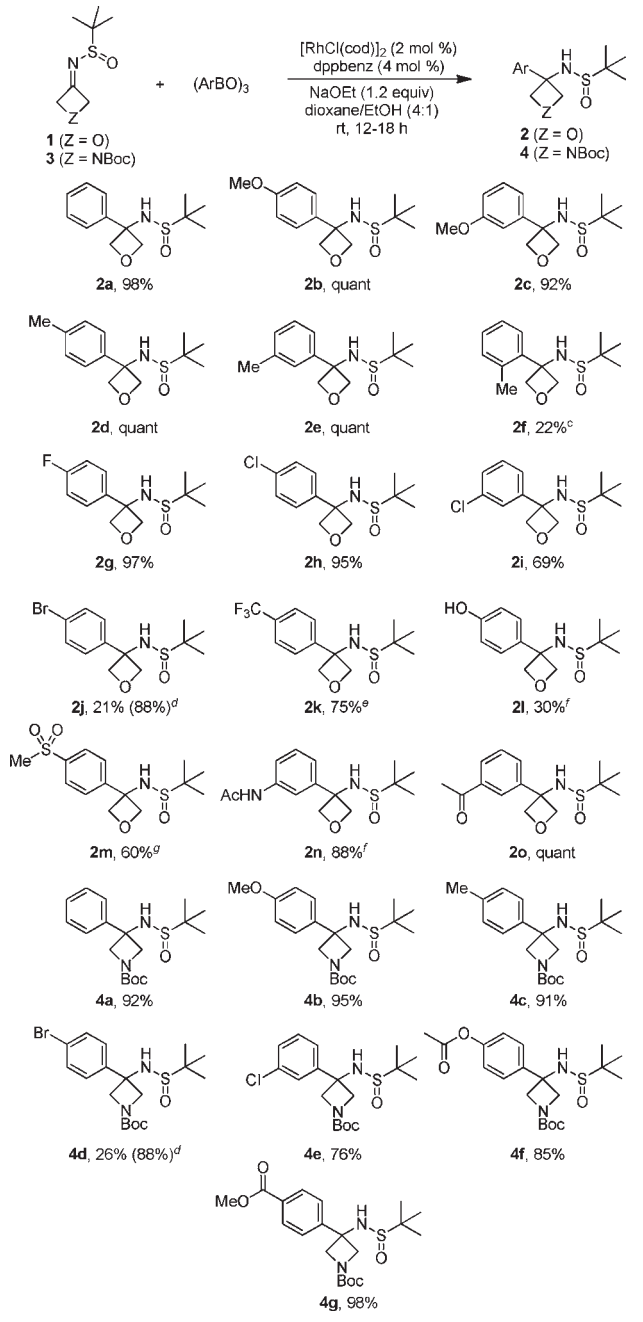
(8) For the preparation of 3-aminooxetanes by the addition of a variety of organolithium reagents to *N*-sulfinyl imine **1** prepared from oxetan-3-one, see ref 3g.

(9) (a) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944. (b) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524.

(10) For examples of drug candidates containing the 3-aminooxoindole pharmacophore, see: (a) Decaux, G.; Soupart, A.; Vassart, G. *Lancet* **2008**, *371*, 1624. (b) Shimazaki, T.; Iijima, M.; Chaki, S. *Eur. J. Pharmacol.* **2006**, *543*, 63. (c) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118.

(11) White, J. R.; Price, G. J.; Plucinski, P. K.; Frost, C. G. *Tetrahedron Lett.* **2009**, *50*, 7365.

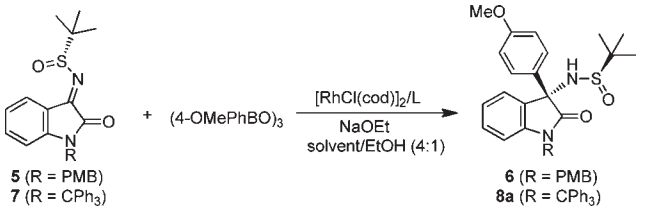
Scheme 1. Oxetane and Azetidine Addition Reaction Scope[a,b]



[a] See Supporting Information for reaction details. [b] Isolated yields after chromatography. [c] Reaction was run at 60 °C. No product was observed at room temperature. [d] Yields in parentheses were obtained from the reaction in the absence of dppbenz. [e] Reaction was run at 60 °C. At room temperature, 50% yield of **2k** was isolated. [f] 3 equiv of NaOEt was used. [g] Reaction was run at 80 °C.

unfavorable steric interactions. All halogen atom-substituted arylboroxines were well tolerated (**2g**–**2j**), although omission of the dppbenz ligand was required to minimize cross-reactivity of the bromo substituent (**2j**). The addition of electron-deficient 4-trifluoromethylphenylboroxine proceeded in high yield when the reaction temperature was increased to 60 °C (**2k**). Additions to ketimine **3** prepared from *N*-Boc-azetidin-3-one[12] also proceeded cleanly and in high yields (**4a**–**4g**). Most importantly, arylboroxines with labile functional groups that are not compatible with Grignard and organolithium reagents can be added to both **1** and **3**, including arylboroxines containing hydroxy (**2l**), sulfonyl (**2m**), anilide (**2n**), ketone (**2o**), alkyl ester (**4g**), and even activated aryl ester (**4f**) functionality.

Table 2. Optimization of Asymmetric Addition Reaction[a]



entry	imine	ligand	solvent	temp (°C)	yield[b] (%)	dr[c]
1	**5**	dppbenz	dioxane	rt	0	–
2		–	dioxane	rt	78	2:1[d]
3	**7**	dppbenz	dioxane	rt	10[e]	–
4		–	dioxane	rt	97	92:8
5		–	dioxane	0	99	93:7
6		–	CH_2Cl_2	0	99	96:4
7		–	THF	0	99	96:4
8		–	toluene	0	17	3:2[d]
9		–	CH_2Cl_2	−20	99	97:3
10		–	THF	−20	99	97:3

[a] General reaction conditions: 4 mol % of rhodium catalyst and/or 4 mol % of dppbenz were used. The reaction time was 18 h. [b] Yields were determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an external standard. [c] Diastereomeric ratio was determined by HPLC unless otherwise specified. [d] Diastereomeric ratio was determined by ^{1}H NMR. [e] 15% of imine **7** remained.

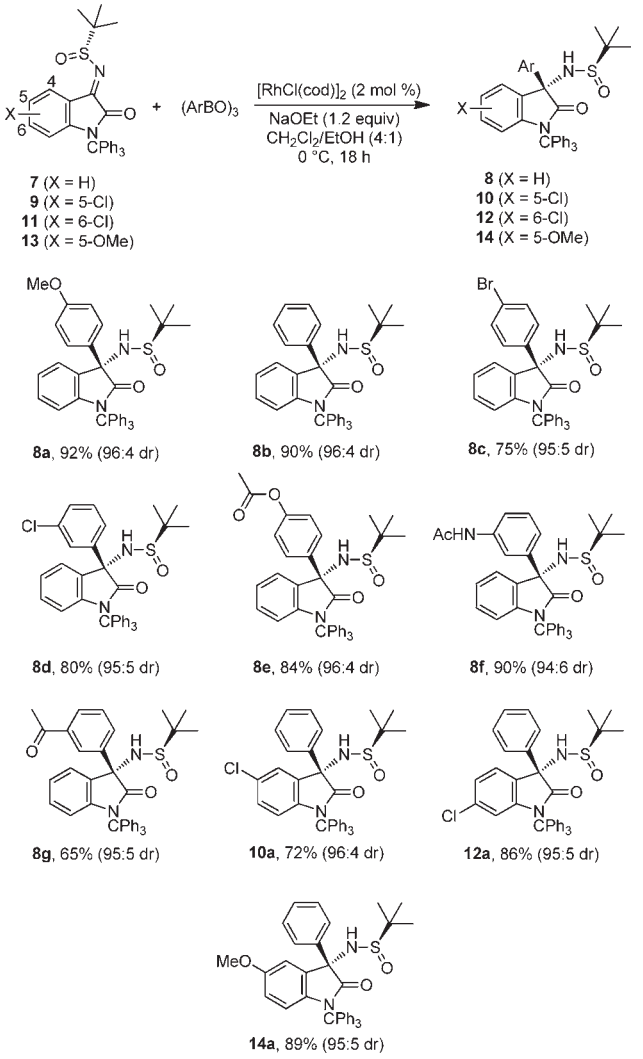
Additions to imines **5**[13] and **7** derived from protected isatins also provide important classes of amine products and allow exploration of the potential for asymmetric induction (Table 2). When the previously optimized reaction conditions from Table 1 were applied to the *N*-PMB-protected imine **5** at room temperature, no conversion was observed (entry 1). However, in the absence of dppbenz the reaction proceeded readily albeit with poor diastereoselectivity (entry 2). Next, because Hayashi and co-workers had observed higher enantioselectivity for copper-catalyzed asymmetric additions of arylboronates to *N*-trityl-protected isatins relative to isatins with other *N*-substituents,[14] *N*-trityl-protected imine **7** was evaluated as a substrate. Interestingly, both excellent conversion to **8a** and high diastereoselectivity was observed for this substrate (entry 4). In addition, complete conversion

(12) For a recent application of imine **3**, see: Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780.

(13) For Grignard reagent addition to isatin imine **5**, see: Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537.

(14) Shintani, R.; Takatsu, K.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6822.

Scheme 2. Reaction Scope of Asymmetric Additions[a−c]



[a] See Supporting Information for reaction details. [b] Isolated yields of the major diastereoisomer after chromatography. [c] Diastereomeric ratio in parentheses was determined by HPLC from the crude products.

continued to be observed at lower temperatures and resulted in notably higher diastereomeric ratios (entries 5−7, 9, and 10). Finally, solvent effects were evaluated. The use of toluene as the cosolvent resulted in both poor conversion and diastereoselectivity, while THF and CH_2Cl_2 provided high yields and diastereoselectivity (entries 6−10).

Under the optimized reaction conditions, different imine substrates and arylboroxines were evaluated to define the reaction scope (Scheme 2). Imine substrates that are electron-neutral (entries **8a**−**8g**), -rich (**14a**), and -deficient (**10a** and **12a**) all reacted with high yields and diastereoselectivities. Electron-neutral and -rich arylboroxines also added readily (e.g., **8a** and **8b**), while electron-deficient arylboroxines displayed a modest decrease in yield (**8g**). As expected, highly functionalized arylboroxines were well tolerated under the reaction conditions (**8e**−**8g**). Moreover, in all cases, the diastereomerically pure major isomer could be isolated by chromatography. Single-crystal X-ray analysis of **8d** established the sense of induction, which, assuming the illustrated sulfinyl imine geometry (Scheme 2), is consistent with the open transition state previously proposed for Rh-catalyzed organoboron reagent additions to aldimines.

In summary, we have developed a highly functional group compatible method for the rhodium-catalyzed addition of readily accessible arylboroxines to activated *N*-*tert*-butanesulfinyl ketimines derived from oxetan-3-one, *N*-Boc-azetidin-3-one, and isatins. The reactions occur readily and in the case of isatin-derived *N*-*tert*-butanesulfinyl ketimines also proceed with excellent diastereoselectivities. The methods reported here should provide access to densely functionalized tertiary carbinamines with considerable pharmaceutical utility.

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Supporting Information Available. Spectroscopic data of all new compounds shown in Schemes 1 and 2, detailed experimental procedures, and HPLC traces and X-ray data for compound **8d** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.