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Enantioselective Rh(I)-Catalyzed Addition of Arylboronic Acids to Cyclic Ketimines

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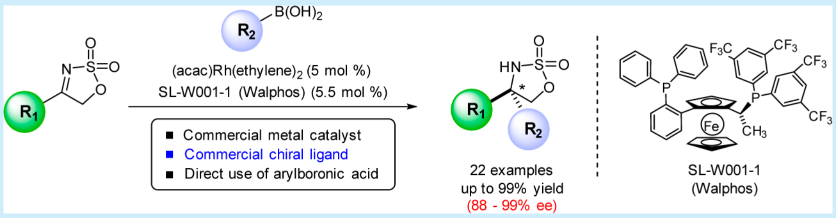
Supporting Information



ABSTRACT: A method for the enantioselective synthesis of chiral α-tertiary amines via Rh-catalyzed 1,2-addition of arylboronic acids to cyclic ketimines is described. The products are efficiently accessed in good yields and excellent enantioselectivities using a commercially available chiral ligand. The reaction scope includes vinyl, aryl, and heteroarylboronic acids with yields ranging from 40% to 99% and enantiomeric excesses from 88% to 99%. Conversion of an addition product into an α,α-diaryl-substituted amino acid is also demonstrated.

Facile synthetic access to chiral α-tertiary amines is an active area of research in the organic chemistry community.[1] Chiral amines are of particular interest to the pharmaceutical industry because this functionality is ubiquitous in pharmacologically active compounds. Although traditional methods for preparing enantioenriched chiral amines, such as chiral acid resolutions and chiral auxiliary-based techniques, continue to be useful,[2] effective catalytic asymmetric processes have the advantages of both synthetic efficiency and atom economy.[3] Transition-metal-catalyzed processes for the preparation of chiral amines are well established and one example is the Rh-catalyzed asymmetric addition of arylboronic acids to aldimines.[4] In contrast, the catalytic enantioselective addition of organometallic reagents to ketimines is significantly less developed.[5] An ongoing interest in our laboratories is the use of cyclic sulfamates as useful synthons for the construction of chiral heterocycles that are typically found in pharmaceuticals. In the course of developing a practical approach to a target piperazinone derivative, we utilized a Pd-catalyzed asymmetric hydrogenation to convert a prochiral cyclic ketimine into a chiral cyclic sulfamate (Figure 1).[6]

As part of this work we also defined a general and robust procedure for the synthesis of these prochiral cyclic ketimine substrates. Based on this earlier research, we were intrigued by the possibility of engaging these intermediates in a Rh-catalyzed asymmetric addition of arylboronic acids to generate the corresponding chiral cyclic sulfamates containing a fully substituted carbon stereocenter.[7,8] More importantly, given the importance of chiral α-tertiary amines in medicinal chemistry programs, a general, reliable, and user-friendly method for the synthesis of chiral α-tertiary amines has been identified as a significant utility within the pharmaceutical industry.

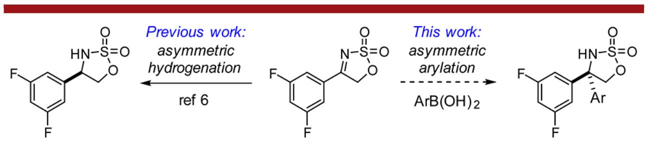
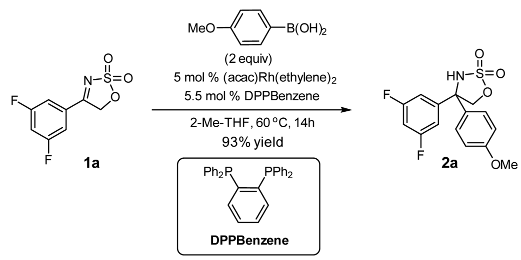


Figure 1. Related prior work and proposed study.

Our initial studies focused on a racemic addition of 4-methoxyphenylboronic acid to 3,4-difluorophenyl substrate **1a** in the presence of a Rh(acac)(ethylene)$_2$ and DPPBenzene in 2-Me-THF (Scheme 1).[2c] Gratifyingly, the reaction resulted in clean conversion to the desired tertiary substituted cyclic sulfamate product **2a** in 93% isolated yield.

To explore the feasibility of an enantioselective variant of this reaction, additions of 4-methoxyphenylboronic acid to 3,4-difluorophenyl substrate **1a** and phenyl substrate **1b** were performed in the presence of chiral phosphine ligands. *With the*

Scheme 1. Initial Racemic Arylation Reaction



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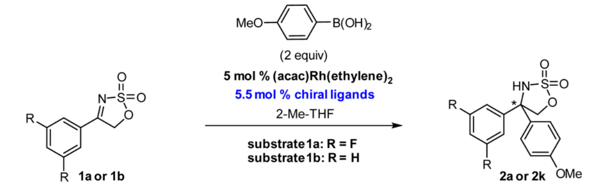
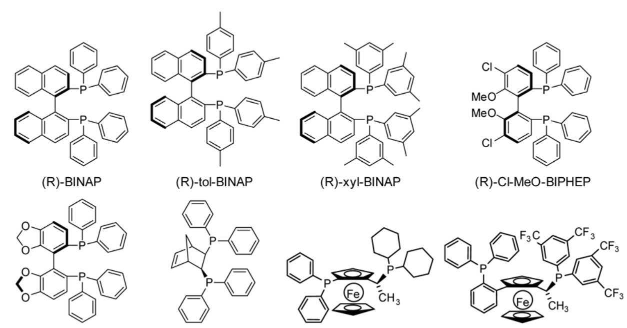
goal of a practical catalytic system in mind, our ligand screening work focused on typical commercially available chiral phosphines.[9] Although reasonable conversions were observed in almost all cases,[10] most of the chiral phosphines in our screen afforded low to moderate enantiocontrol. An exception to this general pattern was SL-W001-1 (Walphos), which provided excellent levels of enantiocontrol for the cyclic ketimine–arylboronic acid combination used for the screen (Table 1).

Table 1. Chiral Ligand Evaluation



entry	ligand[a]	substrate 1a conversion/%	substrate 1a ee/%[b]	substrate 1b conversion/%	substrate 1b ee/%[b]
1	DPPBenzene	99	na	99	na
2	(R)-BINAP	99	-17	99	-25
3	(R)-tol-BINAP	99	24	58	33
4	(R)-xyl-BINAP	99	12	81	2
5	(R)-Cl-MeO-BIPHEP	98	30	58	46
6	(R)-SEGPHOS	91	50	36	61
7	(R,R)-NORPHOS	99	84	51	91
8	SL-J001-1 (Josiphos)	99	42	68	73
9	**SL-W001-1 (Walphos)**	**99**	**97**	**62**	**>99**

[a]Used commercially available phosphine ligands only. [b]Determined by SFC.

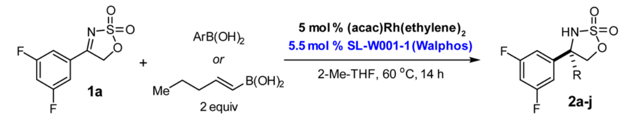


Having established a strong proof-of-concept for the desired asymmetric process, we investigated application of the developed conditions to a range of arylboronic acids and cyclic ketimine substrates. First we studied the reaction of the 3,5-difluorophenylketimine with different arylboronic acids (Table 2). In general, conversion of the imine substrate was good to excellent when 2 equiv of arylboronic acid were employed.[11] Moreover, high levels of enantiocontrol were observed in all cases. Of particular note is the ability to use heteroarylboronic acids such as 2-furylboronic acid (**2f**) and 3-thienylboronic acid (**2h**). In addition, a vinylboronic acid (**2j**) was shown to participate effectively in the developed process albeit with slightly lower enantioselection (88% ee).

Next we studied the scope of cyclic ketimine substrates against several arylboronic acids. The results observed across a variety of cyclic ketimines are shown in Table 3.

In general, electron-deficient cyclic ketimines displayed greater reactivity toward the desired addition process, which allowed for a reduced excess of arylboronic acid to achieve

Table 2. Reactions of 1a with Different Arylboronic Acids



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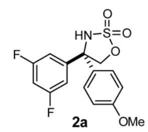
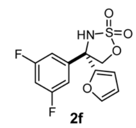
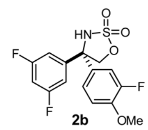
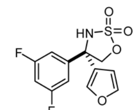
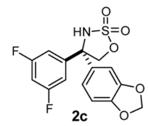
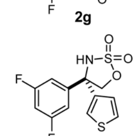
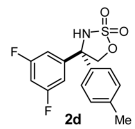
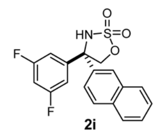
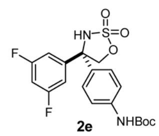
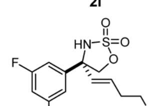
1	 2a	85	97	6[c]	 2f	98	99
2	 2b	90	99	7[c]	 2g	75	>99
3	 2c	86	98	8	 2h	90	>99
4	 2d	83	98	9	 2i	94	>99
5	 2e	90	>99	10	 2j	84	88

[a]Isolated yield. [b]Determined by SFC. [c]3 equiv of arylboronic acid were used.

acceptable conversions. For example, 4-chloro- and 4-carbethoxy-substituted substrates work well with various arylboronic acids. In contrast, electron-rich cyclic ketimines exhibit lower reactivity and typically require up to 3 equiv of arylboronic acid to reach high conversions. Regardless of substrate electronics and reactivity considerations, however, high levels of enantiocontrol were generally observed, with product enantiomeric excesses typically >95%. Of particular note is the observation that aliphatic substrates are viable and provide α,α-alkyl-aryl-substituted products (**2t**–**2v**) in good yields with excellent enantioselectivities.

The absolute configuration of **2b** was determined to be (*S*) by X-ray crystallographic analysis (Figure 2).

To further demonstrate the synthetic utility of the derived chiral cyclic sulfamate products, we elaborated arylation product **2a** into an α,α-diaryl-substituted amino acid (Scheme 2). Reduction of cyclic sulfamate **2a** using Red-Al followed by acidic hydrolysis during workup affords the expected amino alcohol in good yield. After *N*-Boc protection of the amine, one-pot oxidation of the alcohol to the carboxylic acid using the Dess-Martin reagent followed by direct treatment under standard Pinnick-type conditions gave the α,α-diaryl-substituted amino acid **3a** in 70% overall yield (Scheme 2).[12]

In summary, we have developed a novel catalytic system for the asymmetric 1,2-addition of arylboronic acids to a class of cyclic ketimine substrates. Specifically, reaction development within the Merck catalysis facility identified the readily available chiral phosphine ligand Walphos as an excellent ligand for the process. Extremely high levels of enantiocontrol were generally observed, with measured product enantiomeric excesses in most cases >98%. The utility of the derived products was

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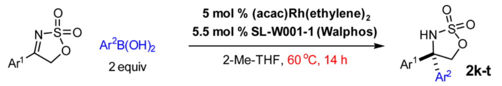
Table 3. Reaction of Different Cyclic Ketimines with Arylboronic Acids



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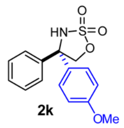
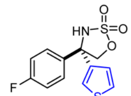
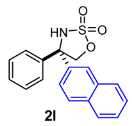
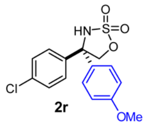
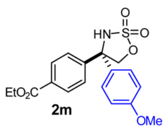
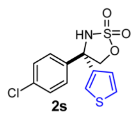
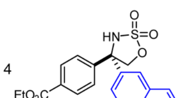
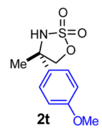
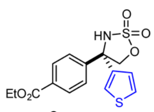
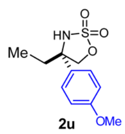
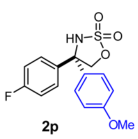
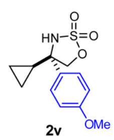
1[c]	 2k	83	>99	7[c]	 2q	69	>99
2[c]	 2l	65	>99	8[c]	 2r	93	>99
3	 2m	97	99	9[c]	 2s	58	>99
4	 2n	94	99	10[c]	 2t	78	93
5	 2o	96	>99	11[c]	 2u	40	96
6[c]	 2p	80	98	12[c]	 2v	82	94

[a]Isolated yield. [b]Determined by SFC. [c]3 equiv of arylboronic acid were used.

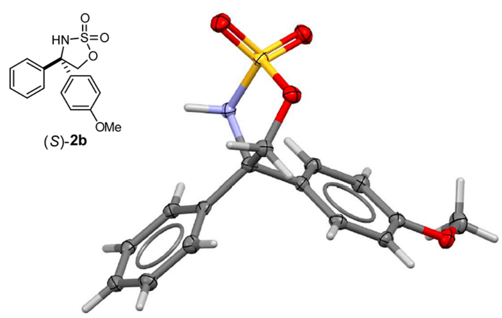
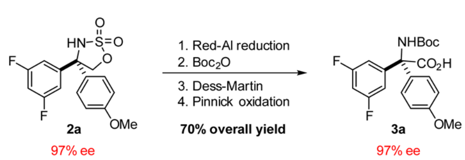


Figure 2. X-ray structure of (*S*)-**2b**.

Scheme 2. Elaboration of Arylation Product 2a



demonstrated by an example of elaboration to an α,α-diaryl-substituted amino acid. Moreover, this practical method will facilitate a structure−activity relationship investigation of chiral α-tertiary amine-containing pharmaceuticals in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02032.

Experimental details, characterization data, and NMR spectra (PDF)

Crystallographic data for (*S*)-**2b** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) To our best knowledge, the use of commercial chiral phosphine for asymmetric Rh(I)-catalyzed addition of arylboronic acids to cyclic ketimines has not been successful due to poor enantioselectivity (see ref 7).

(10) The reaction conversion is sensitive to oxygen or peroxide impurities in the solvent, so it is recommended to employ 2-Me-THF containing BHT inhibitor.

(11) For certain more easily deborylated substrates such as 2-furylboronic acid, it was necessary to use 3 equiv to achieve acceptable conversion.

(12) The enantiomeric excess of the amino acid **3a** was determined via chiral LC and found to be 97%, indicating no erosion occurred during the chemical transformations from **2a**.

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