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Enantioselective Rhodium-Catalyzed Arylation of Cyclic *N*-Sulfamidate Alkylketimines: A New Access to Chiral β-Alkyl-β-aryl Amino Alcohols

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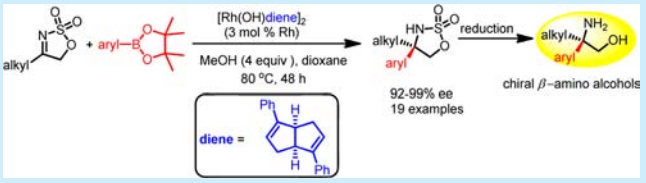
Supporting Information

ABSTRACT: The enantioselective rhodium-catalyzed 1,2-addition of arylboronates to cyclic *N*-sulfamidate alkylketimines was developed. With a rhodium/diene complex as catalyst, high enantioselectivity and broad functional group tolerance were observed. The resulting sulfamidates can easily be converted into chiral β-alkyl-β-aryl amino alcohols.



Chiral β-amino alcohols constitute broadly useful building blocks for the preparation of complex molecules[1] as well as ligands[2] and auxiliaries[3] for asymmetric synthesis. A variety of methods have been developed for their asymmetric synthesis,[4] including asymmetic hydrogenation,[5] asymmetric nucleophilic addition to C═N or C═O double bonds,[6] asymmetric aminohydroxylation,[7] and catalytic asymmetric ring-opening of epoxides.[8] However, only limited success has been achieved in the synthesis of β-alkyl-β-aryl amino alcohols, which are the key intermediates for many bioactive molecules, such as the opioid drug fedotozine (**1**)[9] and β-secretase (BACE) inhibitor (**2**) (Figure 1).[10]

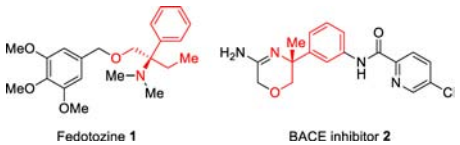
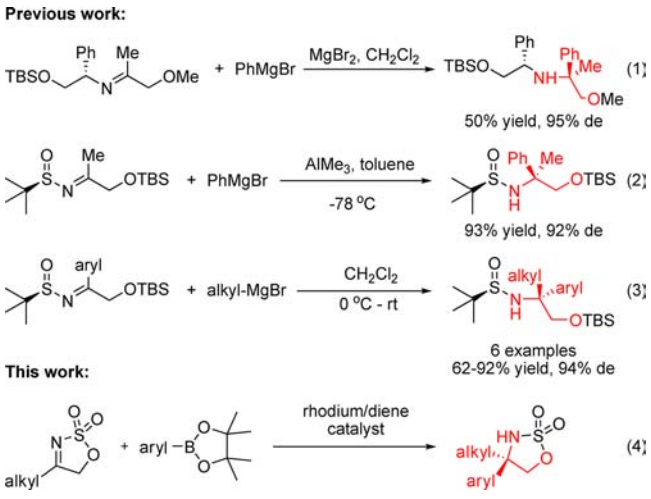


Figure 1. Representative bioactive chiral β-alkyl-β-aryl amino alcohol derivatives.

Previous synthetic methods mainly relied on a chiral auxiliary strategy, in which reactive organomagnesium or -lithium reagents were used in the addition to α-hydroxyl ketone derived imines. For example, Spero and co-workers reported the addition of phenylmagnesium bromide to hydroxyacetone-derived chiral imine, affording the addition product in 50% yield with 95% de (eq 1).[11] Ellman and co-workers achieved improved reaction yield and similar diastereoselectivity by using a chiral *tert*-butanesulfinyl auxiliary (eq 2).[12] Because of the existence of steric hindrance and competing deprotonation at the α-position of these ketimines, the use of arylmetallic reagents may suffer from low reaction yields in this transformation.[13] Delgado, Fustero, and co-workers applied an alternative synthetic approach, in which more reactive alkylmagnesium bromide was used in the addition to *tert*-butanesulfinyl arylketimines to achieve a broader substrate scope (eq 3).[10a] Although the asymmetric catalytic version of this reaction is attractive, and the rapid development of transition-metal-catalyzed addition of organometallic reagents to imines affords an obvious choice to this end,[14,15] the efficient installation of such quaternary chiral centers is often quite challenging because of the steric constraints of ketimines.[15]



Recently, the rhodium-catalyzed imine addition has been greatly promoted by the introduction of chiral olefin ligands[16] and reactive cyclic *N*-sulfonyl and *N*-sulfamidate imines. The rhodium-catalyzed asymmetric alkenylation and allylation of these cyclic imines catalyzed by rhodium/diene were achieved by Lam and co-workers,[17] and the corresponding highly enantioselective arylation reactions were reported by Nichimura, Hayashi, and co-workers[18] as well as Xu and co-workers,[19] using a rhodium/diene and rhodium/sulfur−olefin

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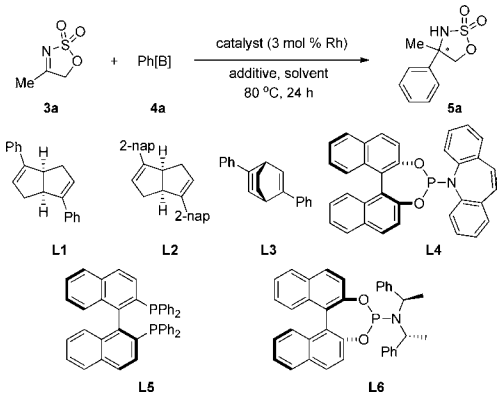
Table 1. Optimization of Reaction Conditions[a]



entry	Ph[B]	catalyst	additive	solvent	yield[b] (%)	ee[c] (%)
1	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L1**	aq KF	toluene	11	92
2	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L2**	aq KF	toluene	5	81
3	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L3**	aq KF	toluene	13	−43
4	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L4**	aq KF	toluene	3	−39
5	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L5**	aq KF	toluene	1	−27
6	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(C_2H_4)_2]_2$/**L6**	aq KF	toluene	1	31
7	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[RhCl(\mathbf{L1})]_2$	aq KF	toluene	10	93
8	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[Rh(OH)(\mathbf{L1})]_2$	aq KF	toluene	32	91
9	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[Rh(OH)(\mathbf{L1})]_2$		toluene	27	92
10	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[Rh(OH)(\mathbf{L1})]_2$		toluene	23	92
11	$PhB(OH)_2$ ($\mathbf{4a_1}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	toluene	39	92
12	$PhBF_3K$ ($\mathbf{4a_2}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	toluene	22	89
13	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	toluene	51	89
14	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	THF	28	93
15	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	dioxane	77	93
16	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	EtOH	dioxane	16	92
17	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	^{i}PrOH	dioxane	18	90
18[d]	PhBPin ($\mathbf{4a_3}$)	$[Rh(OH)(\mathbf{L1})]_2$	MeOH	dioxane	99	95

[a]Reactions were carried out with **3a** (0.1 mmol), **4a** (0.2 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0015 mmol) and chiral ligand (0.0033 mmol) or rhodium complex (0.0015 mmol), and 0.2 M aq KF (0.02 mmol) or alcohol (0.4 mmol) in solvent (1 mL) at 80 °C for 24 h unless otherwise noted. [b]Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]Determined by chiral HPLC analysis. [d]Reaction time was prolonged to 48 h. Isolated yield.

catalyst, respectively. Despite these advancements, most of these reaction focused on the utilization of arylimines, and only one single example with alkylimine was involved in Lam's rhodium-catalyzed allylation research.[17b] Inspired by our recent success in the arylation of unstable alkylimines,[20] we initiated research on the arylation of cyclic *N*-sulfamidate alkylketimine to provide a convenient access to chiral *β*-alkyl-*β*-aryl amino alcohols.

Initially, we examined the addition of phenylboronic acid $\mathbf{4a_1}$ to imine **3a** in the presence of $[RhCl(C_2H_4)_2]_2$ and selected ligands (Table 1). With bicyclo[3.3.0]octadiene **L1**[21] as a ligand, the desired product was produced in high enantioselectivity (92% ee) but only with 11% yield after 24 h reaction (entry 1). The replacement of the phenyl groups on the double bonds with two sterically more hindered 2-naphthyl groups gave rise to the loss in not only reaction yield but also enantioselectivity (entry 2). Chiral diene **L3**[22] bearing a bicyclo[2.2.2]octadiene skeleton showed similar reactivity but aroused significant loss in enantioselectivity (entry 3). Phosphine-containing ligands, including phosphine−olefin **L4**,[23] bisphosphine **L5**, and phosphoramidite **L6**, gave only a trace amount of product with low enantioselectivities (entries 4−6). As expected, the prepared rhodium complex $[Rh(OH)(\mathbf{L1})]_2$ showed higher catalytic activity, affording a reaction yield of 32% (entry 8). Considering the existence of the protodeboronation,[24] efforts to reduce this side reaction by removal of base and a change of proton sources were conducted. However, only a slightly improved reaction yield was observed (entries 8−11), which prompted us to test more stable arylboron reagents. To our delight, when phenylboronic acid pinacol ester $\mathbf{4a_3}$ was used, the reaction yield could be improved to 51% (entry 13). Further reaction condition screening revealed that dioxane was a better solvent, and a prolonged reaction time is necessary to drive the reaction toward completion, providing the desired product in 99% isolated yield with 95% ee (entry 18).

Having identified optimized reaction conditions, we began to explore the substrate scope. The results are summarized in Scheme 1. In all cases, high enantioselectivities were observed (92 → 99% ee). The reaction yield seemed to be sensitive to the steric and electronic properties of both arylboronate esters and imines and varied dramatically. While arylboronate ester with an electron-donating group at the *para* position of the phenyl ring gave moderate to excellent yields (**5b−g**), even the introduction of a mild electron-withdrawing group such as Cl or CO_2Me resulted in a significant loss in reaction yield (**5h−j**).

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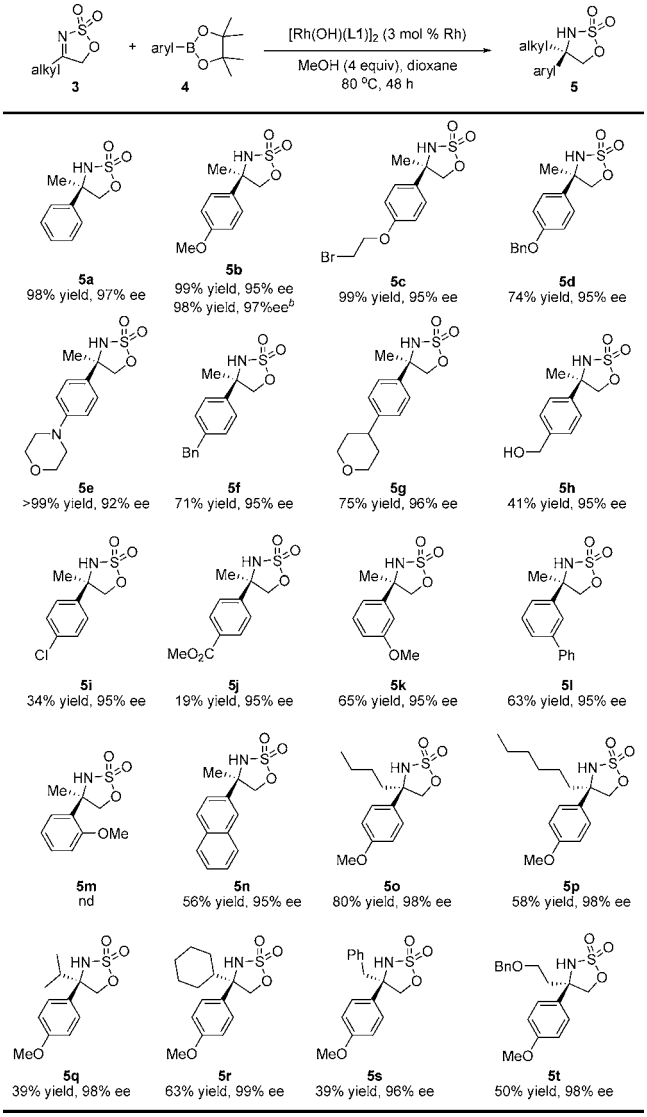
Scheme 1. Reaction Scope for the Rhodium-Catalyzed Asymmetric Arylation of Cyclic *N*-Sulfamidate Imines[a]



[a]Reaction conditions: Reactions were carried out with **3** (0.1 mmol), **4** (0.2 mmol), [Rh(OH)(**L1**)]$_2$ (0.0015 mmol), and MeOH (0.4 mmol) in dioxane (1 mL) at 80 °C for 48 h. Yields refer to isolated product. Enantiomeric excesses were determined by chiral HPLC analysis. [b]2 mmol reaction scale.

Sterically more hindered *meta*-substituted boronate esters gave moderate reaction yields (**5k** and **5l**), but an *ortho*-MeO substituted boronate ester failed to produce any observable product (**5m**). Although replacing the methyl group would increase the sterics of imine substrates and decrease their reactivity, the reaction still proceeded to provide the desired products in decent yields with higher enantioselectivities (**5o**–**t**). It should be noted that a variety of functional groups could be tolerated in this reaction, such as an alkyl bromide (**5c**), a free benzyl alcohol (**5h**), and an ester group (**5j**), which may be problematic functional groups in reactive metallic reagent addition but are convenient handles for further functionalization. A maintained high yield and improved enantioselectivity (**5b**) were obtained with a larger reaction scale (2 mmol of **3a**) compared with a small-scale reaction. The absolute configuration of the product was determined by a single-crystal X-ray analysis of enantiopure **5c** as depicted in Figure 2.

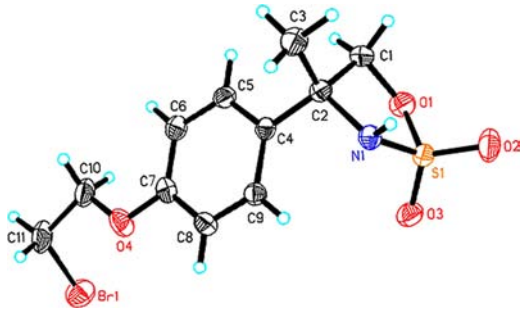
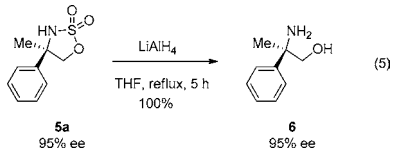


Figure 2. X-ray crystal structure of product **5c**.

The reaction products can easily be converted into the corresponding chiral β-amino alcohol. For example, sulfamidate **5a** was treated with $LiAlH_4$ to afford the β-amino alcohol **6** in quantitative yield and without any loss of optical purity (eq 5).



In summary, an enantioselective 1,2-addition of arylboronate ester to cyclic *N*-sulfamidate alkylketimines was developed with a chiral rhodium/diene complex as a catalyst. High enantioselectivity and broad functional group tolerance were observed in this reaction. The resulting sulfamidates can easily be reduced, providing a convenient alternative to access biologically interesting chiral β-alkyl-β-aryl amino alcohols.[25]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(25) See two preliminary results of the addition to aryl cyclic imines in the Supporting Information.