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Rhodium-Catalyzed Asymmetric Arylation of Cyclic *N*-Sulfonyl Aryl Alkyl Ketimines: Efficient Access to Highly Enantioenriched α-Tertiary Amines

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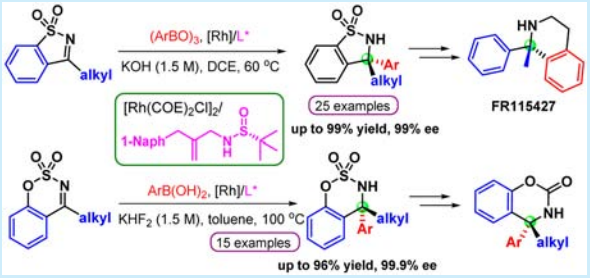
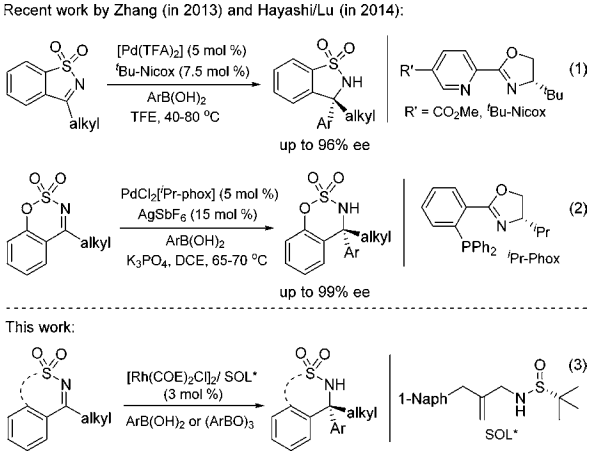
Supporting Information

ABSTRACT: A simple catalyst system of Rh(I)/sulfur-olefin with exceptional catalytic performance has been developed for the highly enantioselective arylation of cyclic *N*-sulfonyl aryl alkyl ketimines with arylboroxines/arylboronic acids. Optically active α-arylalkyl-substituted benzosultams and benzosulfamidates which are generally difficult to obtain were easily prepared with excellent stereocontrol (up to 99.9% ee). The synthetic utility of the approach was demonstrated by the facile construction of NMDA antagonist FR115427 and benzoxazinone derivatives. This protocol offers new opportunities for the efficient synthesis of diverse chiral α-tertiary amines.



Transition-metal-catalyzed asymmetric addition of organometallic reagents to imines is a powerful strategy for the straightforward synthesis of chiral methylamines[1,2] that are an important motif present in many natural products, biologically active compounds, and functional organic molecules. Rhodium and palladium catalysis using stable organoboron reagents has received particular interest in recent years.[2] While asymmetric variants of the addition of organoboron reagents to aldimines have been studied intensively,[3] efficient enantioselective access to the corresponding α-tertiary amines is often problematic because of the employment of relatively less reactive ketimines and the difficulties encountered in the control of stereofacial differentiation. Successful examples of asymmetric addition to ketimines are therefore rare.[4−6] In 2010, an important advance involving the enantioselective addition of sodium tetraarylborates to *N*-tosyl ketimines with Rh/diene catalysts was achieved by Shintani and Hayashi.[4b] Since then, several new developments in this area have emerged; however, achieving excellent enantiocontrol with a broad substrate scope still represents a challenging task.

Optically active sultams and sulfamidates bearing an α-stereogenic center in the amine moiety are two intriguing classes of cyclic amines. We[5a,b] and other groups[3i,4d,f,g] have recently demonstrated that the catalytic asymmetric addition of organoboron reagents to cyclic *N*-sulfonyl imines is an efficient method for the synthesis of such compounds. Most notably, high enantioselectivities were recently obtained in the addition of arylboronic acids to alkyl-substituted cyclic *N*-sulfonyl ketimines under palladium catalysis by Zhang[6a] (eq 1) and Hayashi/Lu[6b] (eq 2) using chiral pyridine-oxazoline and phosphine-oxazoline ligands, respectively, affording enantioenriched benzosultams and benzosulfamidates. In continuation of our own exploration



of Rh/SOL-catalyzed asymmetric addition of diverse imines and carbonyl compounds,[5d] we describe herein our development of an elegant catalytic system that exhibits remarkable selectivity in the asymmetric arylation of cyclic *N*-sulfonyl aryl alkyl ketimines, allowing the construction of both α-arylalkyl-substituted benzosultams and benzosulfamidates with excellent enantioselectivities (eq 3).

Initially we chose methyl substituted five-membered *N*-sulfonyl imine **1a** as the substrate and commenced the reaction with 4-methoxyphenylboronic acid (**2a**) using our previously developed sulfur-olefin ligands (SOLs) **L1**−**L3** in KOH (1.5 M)/toluene at 60 °C in the presence of 1.5 mol % of

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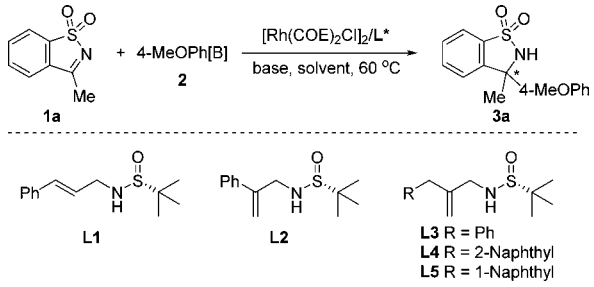
$[Rh(COE)_2Cl]_2$ (Table 1, entries 1−3). As expected, these Rh(I)/SOLs were found to be able to catalyze the reaction.

Table 1. Conditions Optimization for Addition to Ketimine 1a[a]



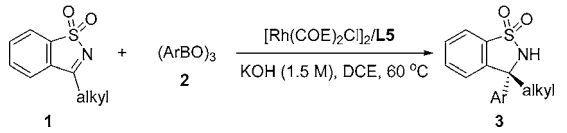
entry	ligand	base (aq)	solvent	yield (%)[b]	ee (%)[c]
1[d]	**L1**	KOH	toluene	13	40
2[d]	**L2**	KOH	toluene	50	81
3[d]	**L3**	KOH	toluene	59	93
4	**L3**	KOH	toluene	99	95
5	**L4**	KOH	toluene	99	96
6	**L5**	KOH	toluene	99	97
7	**L5**	KF	toluene	88	97
8	**L5**	K_2CO_3	toluene	99	97
9	**L5**	K_3PO_4	toluene	95	97
10	**L5**	KOH	dioxane	58	98
11	**L5**	KOH	THF	60	98
12	**L5**	KOH	DCE	99	98
13[e]	**L5**	KOH	DCE	89	98

[a]Conditions: **1a** (0.20 mmol), **2** (boroxine, 1.5 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol %), ligand (3.3 mol %), and base (1.5 M, 0.60 mmol) in 1.0 mL of solvent at 60 °C for 12 h unless otherwise noted. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]4-Methoxyphenylboronic acid (2 equiv) was used. [e]Reaction was performed at rt.

Among them, **L3** exhibited promising enantioselectivity, affording the desired addition product in 59% yield and 93% ee (entry 3). Gratifyingly, when 4-methoxyphenylboroxine (**2b**) was employed instead of 4-methoxyphenylboronic acid, the reaction proceeded with great efficiency and high enantioselectivity (entry 4). Further investigation on ligands disclosed that **L5** bearing a more bulky R (1-naphthyl) group gave the highest enantioselectivity while maintaining the same excellent activity (entry 6). Varying the base did not furnish better results (entries 7−9). Interestingly, under otherwise identical conditions, the use of 1,2-dichloroethane as solvent led to even slightly improved enantioselection (entry 12). In this optimal catalytic system, it is noted that comparable enantioselectivity can be obtained when the reaction was performed at ambient temperature (entry 13).

With the optimized conditions, we examined the scope of the reaction (Table 2). A wide variety of arylboroxines having electron-donating or -withdrawing groups on the phenyl ring reacted smoothly with cyclic *N*-sulfonyl ketimines **1**, providing the addition products α-arylalkyl-substituted benzosultams (**3**) uniformly in high yields and with excellent enantioselectivities (90−99% ee). Of particular note is that the reaction can be effective with a sterically hindered boron reagent bearing an ortho-substituent such as 2-methylphenylboroxine, albeit with a decreased yield (entries 6, 11, 15, 19). Moreover, the reaction enantioselectivity is generally not affected by the alkyl substitution of imine substrates. The aliphatic substituents

Table 2. Rhodium-Catalyzed Asymmetric Arylation of Cyclic Ketimines 1[a]



entry	alkyl	Ar	3	yield[b] (%)	ee[c,d] (%)
1	Me	4-MeOC_6H_4	**3a**	99	98
2	Me	C_6H_5	**3b**	99	98
3	Me	4-MeC_6H_4	**3c**	99	98
4	Me	4-ClC_6H_4	**3d**	99	98
5	Me	3-MeOC_6H_4	**3e**	88	98
6	Me	2-MeC_6H_4	**3f**	66	90
7	Et	4-MeOC_6H_4	**3g**	97	99
8	Et	C_6H_5	**3h**	95	99
9	Et	4-ClC_6H_4	**3i**	99	99
10	Et	3-MeOC_6H_4	**3j**	99	98
11	Et	2-MeC_6H_4	**3k**	77	99
12	^{n}Bu	C_6H_5	**3l**	99	99
13	^{n}Bu	4-ClC_6H_4	**3m**	99	99
14	^{n}Bu	3-MeOC_6H_4	**3n**	91	99
15	^{n}Bu	2-MeC_6H_4	**3o**	41	92
16	Bn	4-MeOC_6H_4	**3p**	99	99
17	Bn	C_6H_5	**3q**	99	99
18	Bn	3-MeOC_6H_4	**3r**	99	98
19	Bn	2-MeC_6H_4	**3s**	66	99
20	^{i}Pr	4-MeOC_6H_4	**3t**	98	99
21	Cyclopentyl	4-MeOC_6H_4	**3u**	99	98
22	Cy	C_6H_5	**3v**	99	99
23	Cy	4-ClC_6H_4	**3w**	99	99
24	Cy	3-MeOC_6H_4	**3x**	99	99
25	Cy	4-FC_6H_4	**3y**	97	99

[a]Conditions: **1** (0.20 mmol), **2** (1.5 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol %), ligand (3.3 mol %), and KOH (1.5 M, 3.0 equiv) in 1.0 mL of DCE at 60 °C for 12 h. [b]Isolated yields. [c]Determined by HPLC. [d]The absolute stereochemistry was determined by comparing the $[\alpha]_D$ with known data.[6a]

could include a broad range of groups including methyl, ethyl, butyl, benzyl, isopropyl, cyclopentyl, and cyclohexyl. To our knowledge, these results are among the best in the asymmetric addition of organoboron reagents to alkyl-substituted cyclic *N*-sulfonyl ketimines.

Having established the highly enantioselective arylation of five-membered *N*-sulfonyl ketimines, we turned our attention to six-membered ring imines for a similar addition, which could lead to chiral benzosulfamidates. In general, six-membered cyclic imines are considered to be less reactive than five-membered ones. To test if the aforementioned conditions are applicable, we conducted the reaction with ketimine **4a** bearing a methyl group attached to the imine carbon as the substrate. To our disappointment, only a trace amount of product formation was observed (Table 3, entry 1). After some careful experiments, we were delighted to find that the reaction can be promoted at 80 °C in *tert*-amyl alcohol/dioxane in the presence of solid K_2CO_3 (3 equiv), giving a 65% isolated yield of the expected adduct benzosulfamidate **5a** with an extremely high enantioselectivity (99.7% ee) (entry 4). Interestingly, the use of 4-methoxyphenyl boronic acid (2 equiv) in combination with KHF_2 (1.5 M) in toluene at 80 °C produced **5a** in an improved yield (75%) with equally high enantioselectivity (99.9% ee) (entry 5). While the

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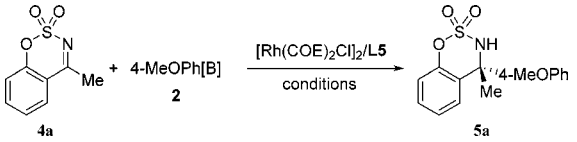
Table 3. Conditions Optimization for Addition to Ketimine 4a[a]



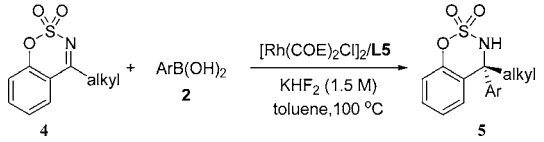
entry	2 Ar[B][b]	conditions	yield (%)[c]	ee (%)[d]
1	$(ArBO)_3$	KOH (1.5 M), DCE	trace	–
2	Ar_4BNa	MeOH/dioxane	trace	–
3[g]	$(ArBO)_3$[e]	K_3PO_4, *tert*-AmylOH/dioxane	49	98.6
4[g]	$(ArBO)_3$[e]	K_2CO_3, *tert*-AmylOH/dioxane	65	99.7
5[g]	$ArB(OH)_2$	KHF_2 (1.5 M), toluene	75	99.9
6[h]	$ArB(OH)_2$[f]	KHF_2 (1.5 M), toluene	89	99.9

[a]Conditions: **4a** (0.10 mmol), **2** (2.0 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol %), ligand (3.3 mol %), and salt (3.0 equiv) in 1.5 mL of solvent at 60 °C for 24 h unless otherwise noted. [b]Ar = 4-MeOPh. [c]Isolated yields. [d]Determined by HPLC. [e]0.67 equiv. [f]3 equiv. [g]80 °C. [h]100 °C.

reaction was carried out with 3 equiv of boronic acid at 100 °C, the corresponding **5a** can be obtained in both very good yield (89%) and enantioselectivity (99.9% ee) (entry 6).

Under the newly optimized reaction conditions, the substrate scope was evaluated. As summarized in Table 4, all excellent

Table 4. Rhodium-Catalyzed Asymmetric Arylation of Cyclic Ketimines 4[a]



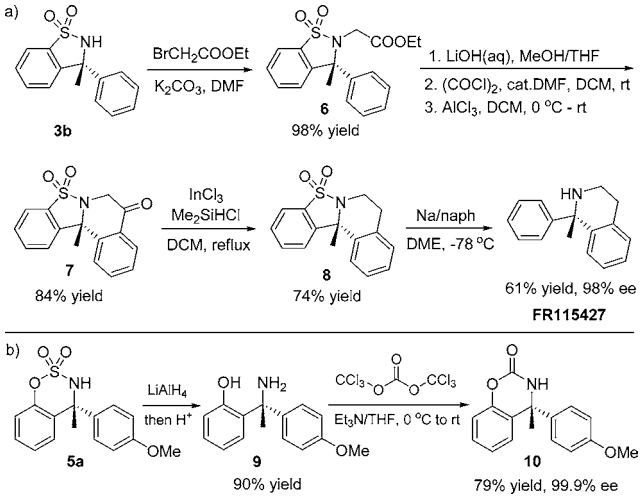
entry	alkyl	Ar	5	yield[b] (%)	ee[c,d] (%)
1	Me	4-$MeOC_6H_4$	**5a**	89	99.9
2	Me	3-$MeOC_6H_4$	**5b**	75	99.8
3	Me	2-$MeOC_6H_4$	**5c**	17	99.3
4	Me	4-MeC_6H_4	**5d**	79	99.8
5	Me	C_6H_5	**5e**	76	99.8
6	Me	3-MeC_6H_4	**5f**	63	97.6
7	Me	4-FC_6H_4	**5g**	47	99.5
8	Me	4-$MOMOC_6H_4$	**5h**	75	99.8
9	Me	2-naphthyl	**5i**	62	99.9
10	Me	3-thienyl	**5j**	74	99.6
11	Me	2-furanyl	**5k**	49	98.5
12	Et	4-$MeOC_6H_4$	**5l**	96	99.6
13	Et	C_6H_5	**5m**	82	99.8
14	^{n}Bu	4-$MeOC_6H_4$	**5n**	78	99.9
15	^{n}Bu	C_6H_5	**5o**	72	99.9

[a]Conditions: **4** (0.10 mmol), **2** (3.0 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol %), ligand (3.3 mol %), and KHF_2 (1.5 M, 3.0 equiv) in 1.5 mL of toluene at 100 °C for 24 h. [b]Isolated yields. [c]Determined by HPLC. [d]The absolute stereochemistry was determined by comparing the $[\alpha]_D$ with known data.[6b]

enantioselectivities (97.6–99.9% ee) were observed with a wide range of arylboronic acids regardless of the substitution pattern (entries 1–9), although sterically hindered 2-methoxyphenylboronic acid afforded a low yield (entry 3). The reaction also proceeded with great enantiomeric control when heteroboronic acids such as 3-thienyl and 2-furanyl boronic acids were employed (entries 10, 11). In addition to methyl-substituted ketimine **4a**, those bearing ethyl and butyl were also suitable substrates for this arylation, giving the corresponding enantiomerically pure benzosulfamidate products **5l–5o** (entries 12–15). Using the same conditions, we further examined the addition of 4-methylphenylboronic acid to phenyl-substituted ketimine **4**[5a] and found that a relatively high enantioselectivity (91% ee) could be obtained, but the yield was not ideal (38%).

To highlight the synthetic utility, we have applied this methodology in the synthesis of a series of biologically interesting compounds. For example, treatment of benzosultam **3b** with ethyl bromoacetate followed by Friedel–Crafts cyclization furnished the tetracyclic sulfonamide intermediate **7** bearing a tetrasubstituted carbon stereogenic center on the ring. Subsequently, compound **7** was converted to **8** first and then underwent sultam ring cleavage under the conditions of sodium naphthalenide, providing an efficient asymmetric synthesis of FR115427,[7] a tetrahydroisoquinoline compound that was developed as an NMDA antagonist to prevent ischemia-induced neuronal degeneration (Scheme 1a). In the other case, ring

Scheme 1. Synthesis of the α-Tertiary Amine Derivatives



opening of benzosulfamidate **6a** with $LiAlH_4$ gave the corresponding phenolic methylamine intermediate **9**, which was subjected to triphosgene/Et_3N to produce benzoxazinone derivative **10** without losing optical purity (Scheme 1b). The benzoxazinone compounds have been reported with PKM2 activities to treat neoplastic disorders.[8]

In summary, we have developed an efficient rhodium-catalyzed asymmetric arylation process. Challenging cyclic *N*-sulfonyl aryl alkyl ketimines reacted smoothly with organoboron reagents in the presence of a simple chiral sulfur-olefin ligand to give α-arylalkyl-substituted benzosultams and benzosulfamidates with excellent stereocontrol (up to 99.9% ee). In contrast to known reports,[6] this method is quite advantageous in terms of simplicity of the catalytic system. It is also noteworthy that the results particularly for benzosultams are superior. Further studies of the synthetic utilities of this protocol reveal it to be a promising method for the synthesis of many other valuable amine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization. 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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