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Construction of Cyclic Sulfamidates Bearing Two *gem*-Diaryl Stereocenters through a Rhodium-Catalyzed Stepwise Asymmetric Arylation Protocol

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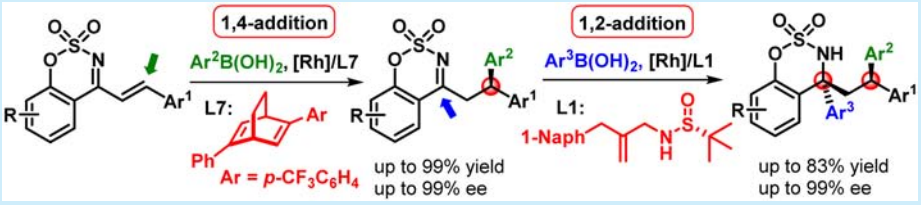
Supporting Information



ABSTRACT: A rhodium-catalyzed stepwise asymmetric 1,4- and 1,2-addition of arylboronic acids to α,β-unsaturated cyclic *N*-sulfonyl ketimines has been developed, providing a wide range of *gem*-diaryl-substituted chiral benzosulfamidates with high optical purities. C_1-Symmetric chiral diene and branched chiral sulfur−olefin ligands were sequentially utilized in this double-arylation process for high stereocontrol. Further synthetic utility offers new opportunities for the facile construction of otherwise difficult to access polycyclic heterocycles.

Rhodium-catalyzed asymmetric 1,4-conjugate addition of organoboron reagents to electron-deficient olefins has been recognized as one of the most powerful C−C bond formation approaches to access versatile enantiomerically enriched compounds since the pioneering work of Hayashi and Miyaura in 1998.[1,2] After nearly two decades of effort, impressive advances have been made in developing highly effective chiral catalysts/ligands, with α,β-unsaturated ketones/esters/amides being among the most intensively investigated substrates. Nonetheless, although α,β-unsaturated imines are another common set of potential compounds that could be subjected to 1,4-addition to afford valuable chiral building blocks, catalytic enantioselective processes are exceptionally rare,[3] probably due to the intrinsic lower 1,4-addition reactivity of α,β-unsaturated imines and the difficulty in the regio- and enantiocontrol of 1,2-/1,4-addition. To the best of our knowledge, until now there has been only one successful example of rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated *N*,*N*-dimethylsulfamoyl imino esters using chiral bicyclic bridgehead phosphoramidite ligands, providing γ,γ-diaryl-α,β-dehydroamino esters with good to high enantiomeric excesses.[4] Thus, efficient enantioselective 1,4-conjugate addition to α,β-unsaturated imines remains challenging and underdeveloped. Critical to this success is the discovery of proper chiral ligands.

Cyclic sulfamidates are versatile synthetic intermediates in organic synthesis and structurally important core units found in many biologically active compounds.[5] Recently, we[6] and others[7] have been engaged in the development of new catalytic asymmetric procedures for the generation of enantioenriched cyclic *N*-sulfonylamines including sulfamidates.[6a−c,7b−f,h,i] A number of cyclic *N*-sulfonylimines were employed in rhodium-catalyzed enantioselective addition of organoboron reagents. Recognizing that six-membered ring imines are relatively less reactive toward the organoboron addition, we speculated that their corresponding α,β-unsaturated cyclic ketimines might undergo 1,4-conjugate addition preferably at the more reactive C═C bond in a highly enantiocontrolled manner with the appropriate selection of chiral ligands. If this regio- and enantioselective process could take place, the resulting aryl alkyl ketimines, upon further stereoselective 1,2-addition by different nucleophiles and ring cleavage of cyclic sulfamidates, would afford α,γ-functionalized diverse chiral tertiary amines having two interesting stereogenic centers. Herein, we describe our success of a catalytic stereoselective double arylation of α,β-unsaturated cyclic *N*-sulfonyl ketimines through rhodium-catalyzed sequential 1,4-/1,2-addition reactions with arylboronic acids, allowing the construction of benzosulfamidates bearing two *gem*-diaryl stereocenters with excellent enantioselectivities (Scheme 1).

Our initial study began with the reaction of styryl-substituted six-membered cyclic *N*-sulfonyl imine **1a** and *p*-tolylboronic acid **2a** in KHF_2 (1.5 M)/toluene at 100 °C in the presence of 2.5 mol % of $[Rh(COE)_2Cl]_2$ and 5 mol % of our previously developed branched chiral sulfur olefin **L1**, which has been demonstrated as an elegant ligand in rhodium-catalyzed 1,2-addition of cyclic *N*-

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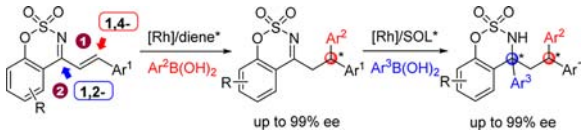
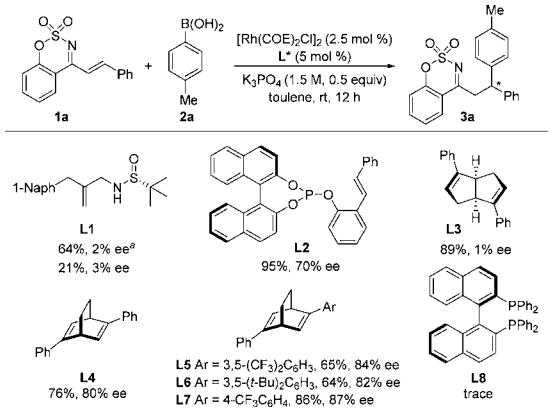
Scheme 1. Stepwise 1,4-/1,2-Addition Strategy for the Synthesis of Benzosulfamidates with Two *gem*-Diaryl Stereocenters



sulfonyl ketimines.[6a] As expected, the rhodium complex with **L1** facilitated the regioselective 1,4-addition to produce the corresponding *β-gem*-diaryl-substituted ketimine **3a** in a good yield (64%), albeit with almost no enantioselection (Scheme 2).

Scheme 2. Ligand Screening



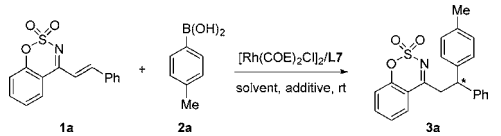
[a]The reaction was carried out with KHF_2 at 100 °C.

In contrast to Kim's work,[4] no formation of the enamine product as well as the 1,2-adduct was observed. While changing the base to K_3PO_4 and lowering the temperature did not improve the enantioselectivity, a number of different chiral olefin ligands (**L2**–**L7**) that are available in our laboratory were screened. Interestingly, the phosphite–olefin ligand **L2**[8] exhibited excellent catalytic reactivity and moderate enantioselectivity (95% yield, 70% ee), and promising results (76% yield, 80% ee) were attained using Hayashi's bicyclo[2.2.2]octadiene **L4**.[9] Through further evaluation of unsymmetrically substituted chiral [2.2.2]dienes,[10,11] we discovered that the use of ligand **L7** bearing a *p*-CF_3 substituent could lead to exclusive 1,4-addition product **3a** in both good yield (86%) and a high level of enantioselection (87% ee).

Encouraged by the promising result obtained with chiral diene ligand **L7**, further investigations on solvent, additives, and catalyst loading were carefully conducted (Table 1). Varying the solvent did not furnish better results (entries 1–6). Among the various additives screened (entries 7–11), K_2HPO_4 was found to be the best one and gave both the highest yield (99%) and enantioselectivity (93% ee) (entry 11). Notably, reducing the catalyst loading would only cause marginal erosion of the reaction yield (entry 12).

With the optimized conditions in hand, we proceeded to examine the reaction substrate scope (Table 2). A range of arylboronic acids with varying electronic and steric demands were successfully reacted with cyclic *N*-sulfonyl imine **1a** to give the corresponding 1,4-adducts **3** in good yields with high enantioselectivities (83–99% ee) (entries 1–11). Remarkably, extremely high enantioselectivities (99% ee) as well as excellent yields (95–98%) were obtained with more sterically hindered

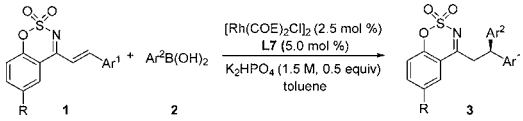
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	additive[b]	yield[c] (%)	ee[d] (%)
1	toluene	K_3PO_4	86	87
2	dioxane	K_3PO_4	56	57
3	THF	K_3PO_4	18	48
4	DCE	K_3PO_4	16	61
5	DCM	K_3PO_4	21	87
6	MeOH	K_3PO_4	98	83
7	toluene	KOH	76	91
8	toluene	K_2CO_3	62	93
9	toluene	Et_3N	55	90
10	toluene	KH_2PO_4	34	92
11	toluene	K_2HPO_4	99	93
12[e]	toluene	K_2HPO_4	88	92

[a]The reaction was carried out with 0.2 mmol of cyclic imine **1a** and 2.0 equiv of *p*-tolyboronic acid **2a** in the presence of 5 mol % of [Rh]/**L7** with 1.0 mL of solvent at rt for 12 h. [b]Unless noted, 0.5 equiv of additive (1.5 M) was used. [c]Isolated yield. [d]Determined by Chiral HPLC. [e]The reaction was carried out in the presence of 3 mol % of [Rh]/**L7**.

Table 2. Rh-Catalyzed Asymmetric 1,4-Addition of *α,β*-Unsaturated Ketimines[a]



entry	R	Ar^1	Ar^2	3	yield[b] (%)	ee[c] (%)
1	H	Ph	4-MeC_6H_4	**3a**	99	93
2	H	Ph	4-$MeOC_6H_4$	**3b**	90	93
3[d]	H	Ph	4-ClC_6H_4	**3c**	89	91
4	H	Ph	2-MeC_6H_4	**3d**	96	99
5[e]	H	Ph	2-BrC_6H_4	**3e**	95	99
6	H	Ph	2-FC_6H_4	**3f**	89	85
7	H	Ph	1-naphthyl	**3g**	98	99
8[d]	H	Ph	2-naphthyl	**3h**	90	91
9[e]	H	Ph	3-MeC_6H_4	**3i**	96	83
10	H	Ph	3-$MeOC_6H_4$	**3j**	92	84
11	H	Ph	3,4-$MeOC_6H_3$	**3k**	91	94
12	Me	Ph	1-naphthyl	**3l**	98	98
13	Me	Ph	4-MeC_6H_4	**3m**	70	94
14	Cl	Ph	4-MeC_6H_4	**3n**	92	90
15	H	3-ClC_6H_4	Ph	**3o**	87	82
16	H	3-MeC_6H_4	Ph	**3i′**	99	88
17	H	4-MeC_6H_4	Ph	**3a′**	89	87
18	H	4-MeC_6H_4	1-naphthyl	**3p**	99	99
19	H	2-FC_6H_4	Ph	**3f′**	93	86
20	H	2-FC_6H_4	2-MeC_6H_4	**3q**	99	99

[a]The reaction was carried out with 0.2 mmol of cyclic imine **1** and 2.0 equiv of arylboronic acid **2** in the presence of 5.0 mol % of [Rh], 5.0 mol % of ligand **L7**, and K_2HPO_4 (1.5 M, 0.5 equiv) in 1.0 mL of toluene at rt for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The reaction was carried out at 0 °C. [e]The reaction was carried out at 40 °C.

arylboronic acids bearing a bulky *ortho* substituent (entries 4, 5, and 7). In some cases, the reaction temperature was increased to

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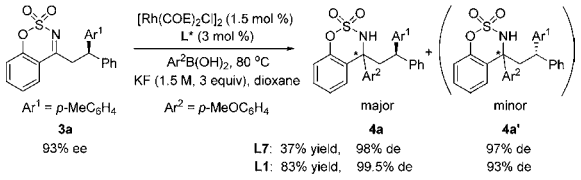
40 °C to achieve better yields (entries 5 and 9). It should be noted that further 1,2-addition of product **3** with 4-chlorophenylboronic acid and 2-naphthylboronic acid was observed at ambient temperature. In these cases, we found that the further conversion could be avoided when the reaction was performed at lower temperature (0 °C) (entries 3 and 8). The scope of α,β-unsaturated imine substrates **1** was also examined. Imines bearing substituents on either phenyl ring were tolerated in this reaction (entries 12−20). Interestingly, both enantiomers of the product could be smoothly accessed by simply switching the acceptor and donor aryl substituents (entries 1 vs 17, 6 vs 19, 9 vs 16).

Having established the highly regio- and enantioselective 1,4-addition of α,β-unsaturated cyclic *N*-sulfonyl ketimines, we turned our attention to test the possibility of further stereospecific 1,2-arylation of 1,4-adducts, which would lead to structurally interesting chiral benzosulfamidates having two *gem*-diaryl stereogenic centers. On the basis of the above findings of further 1,2-addition of product **3** with 4-chlorophenylboronic acid and 2-naphthylboronic acid at ambient temperature and our recent success of enantioselective 1,2-addition of cyclic *N*-sulfonyl aryl alkyl ketimines, we decided to initially conduct the reaction of ketimine **3a** (93% ee) with *p*-methoxyphenylboronic acid **2b** under rhodium catalysis by using **L7** and **L1** as ligands. Following careful experimentation, we found that the expected highly diastereoselective 1,2-addition could take place at higher temperature (80−100 °C) with concomitant formation of four stereoisomers. Further optimization of the reaction conditions led to the ideal results of 1,2-addition (83% yield for **4a** and **4a′** and 99.5% de for **4a**) when sulfur−olefin ligand **L1** was employed in KF/dioxane (1.5 M) at 80 °C (Scheme 3).

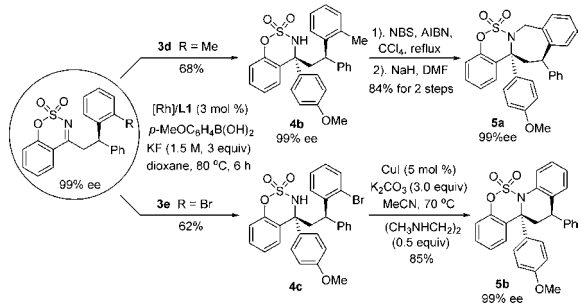
Scheme 3. Diastereoselective 1,2-Addition of Ketimine 3a



With the catalytic system for sequential 1,2-addition identified, we then investigated its applicability in the reactions of aryboronic acid **2b** to highly enantioenriched 1,4-adducts **3d** and **3e** (both with 99% ee). Gratifyingly, both reactions proceeded smoothly to give the desired arylation products **4b** and **4c**[12] as a sole stereoisomer (99% ee). To highlight their synthetic utilities, construction of two intriguing classes of chiral polycyclic heterocycles was carried out. Bromination of **4b** with NBS followed by intramolecular substitution afforded the fused tetrahydrobenzo[*c*]azepine derivative **5a** in 84% yield over two steps without losing optical purity (99% ee) (Scheme 4). In the other case, intramolecular cyclization of **4c** by means of copper-catalyzed coupling generated optically pure tetrahydroquinoline derivative **5b** in 85% yield (Scheme 4). It is worth mentioning that heterocyclic compounds such as **5a** and **5b** consisting of four fused rings bearing a benzosulfamidate skeleton and two *gem*-diaryl stereogenic centers are otherwise difficult to access and might be potentially useful in medicinal chemistry.

Determination of the absolute configuration of the two newly formed carbon stereocenters was carried out by X-ray crystallography of **4b**,[13] which proved to be (*R*,*R*) as indicated in Figure 1. The observed stereochemistry is consistent with the

Scheme 4. Synthetic Transformations of Addition Products



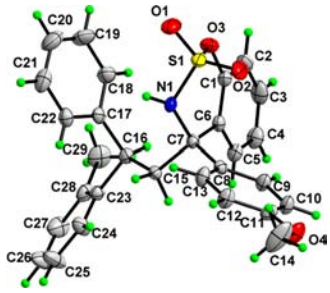
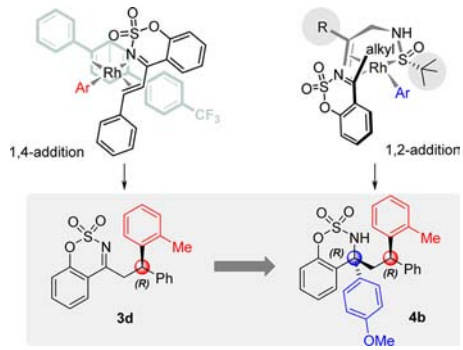


Figure 1. X-ray structure of (*R*,*R*)-**4b**.

proposed transition-state models in which the sulfonyl moiety of the imine substrates orient away from the attached group of the olefin ligands to minimize the steric interaction (Scheme 5). Thus, the stereochemical outcome of other products including 1,4-adducts **3** could be assigned by analogy assuming a same reaction pathway.

Scheme 5. Proposed TS Models for Stereoinduction



Encouraged by the success of highly stereoselective stepwise 1,4- and 1,2-addition of α,β-unsaturated six-membered cyclic *N*-sulfonyl ketimines, we attempted to test the developed catalytic system in the addition with more challenging five-membered ring imines. Under the same conditions indicated in Table 2, reaction of ketimine **6** with *p*-tolylboronic acid **2a** produced the 1,4-adduct **7** with moderate enantioselectivity (75% ee) along with its further arylation product **8** with excellent diastereocontrol (Table 3, entry 1). With prolonged reaction time and increased amounts of arylboronic acid, only the double-arylation product **8** (**8a** and **8a′** are inseparable via column chromatography) was obtained in very good yield (94%) with the same high level of asymmetric induction (95−97% de) (entry 2). Addition of **7** with 2 equiv of *p*-tolylboronic acid could also provide the double-arylation product **8** in comparable yield with same stereoselectivity (entry 3).

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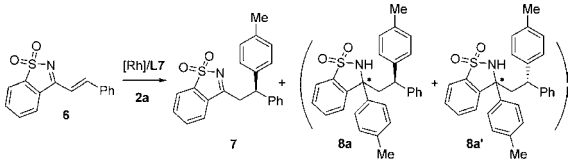
Table 3. Attempts for Addition of Five-Membered Cyclic Imine 6[a]



entry	2a (equiv)	yield[b]/ee[c] (%) of 7	yield (%)[b] of (8a + 8a′)	de (%)[c] of 8a/8a′
1	2	24/75	57	95/97
2[d]	3		94	95/97
3[e]	2		81	95/97

[a]The reaction was carried out with 0.2 mmol of imine **6**, 2.0 equiv of *p*-tolyboronic acid **2a** in the presence of 2.5 mol % of $[Rh(COE)_2Cl]_2$, 5 mol % of **L7**, and K_2HPO_4 (1.5 M, 0.5 equiv) in 1.0 mL of toluene at rt for 12 h, unless noted. [b]Isolated yield. [c]Determined by Chiral HPLC. [d]Reaction for 24 h. [e]The reaction was carried out with **7** (75% ee) as substrate for 12 h.

To summarize, we have developed a rhodium-catalyzed asymmetric double-arylation process of α,β-unsaturated cyclic *N*-sulfonyl ketimines consisting of 1,4-addition and successive 1,2-addition in a highly regio- and enantioselective manner. C_1-Symmetric chiral diene and simple branched chiral sulfur−olefin ligands were sequentially utilized to control the stereoinduction. This protocol enables the efficient synthesis of a range of chiral cyclic amines with concomitant creation of two interesting *gem*-diaryl stereogenic centers. It provides access to two new classes of chiral polycyclic heterocycles. It is also worth noting that such 1,4-addition of α,β-unsaturated cyclic imines is a rare example in rhodium catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01183.

Experimental procedures and spectroscopic data of all new compounds (PDF)

X-ray crystal structure data for (*R*, *R*)-**4b** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) The stereoisomers of 1,2-adduct **4c** are inseparable in HPLC. Therefore, the optical purity of 1,2-addition was finally determined by chiral HPLC analysis of product **5b**.

(13) Crystal data of **4b**: empirical formula, $C_{29}H_{27}NO_4S$; formula weight, 485.57; temperature, 170 K; Mo Kα radiation, wavelength, 0.71073 Å; crystal system, orthorhombic; space group, $P2_12_12_1$; unit cell dimensions: a = 8.3536(10) Å, b = 13.8716(16) Å, c = 21.444(3) Å, θ = 2.6−25.0°; volume = 2484.9(5) Å^3; Z = 4; D_x = 1.298 Mg/m^3; $F(000)$ = 1024; $R[F^2 > 2\sigma(F^2)]$ = 0.043, $wR(F^2)$ = 0.109; Flack parameter, 0.04(5).

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