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Enantioselective Access to Spirocyclic Sultams by Chiral Cp^x–Rhodium(III)-Catalyzed Annulations

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Abstract: Chiral spirocyclic sultams are a valuable compound class in organic and medicinal chemistry. A rapid entry to this structural motif involves a [3+2] annulation of an *N*-sulfonyl ketimine and an alkyne. Although the directing-group properties of the imino group for C–H activation have been exploited, the developments of related asymmetric variants have remained very challenging. The use of rhodium(III) complexes equipped with a suitable atropchiral cyclopentadienyl ligand, in conjunction with a carboxylic acid additive, enables an enantioselective and high yielding access to such spirocyclic sultams.

Chiral sultams are an important class of compounds in organic and medicinal chemistry. They are used as reagents[1] and as chiral auxiliaries[2] in various asymmetric reactions. A number of chiral sultams have potent biological activities with medicinal value[3] and several synthetic approaches,[4] including enantioselective syntheses, have been devised.[5] Chiral spirocyclic sultams have been less investigated, despite biological activities such as γ-secretase inhibition[6] and aldose reductase inhibition (Figure 1).[7] Racemic syntheses of this valuable structural motif have been reported using intramolecular cyclizations of elaborated precursors[8] or transition-metal-catalyzed [3+2] annulations.[9,10] Enantioselective syntheses of spirocyclic sultams are scarce and have so far been limited to one reported organocatalyzed reaction.[11]

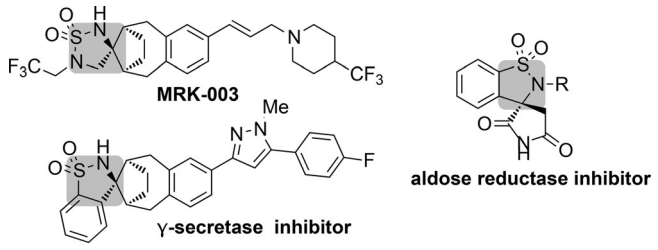
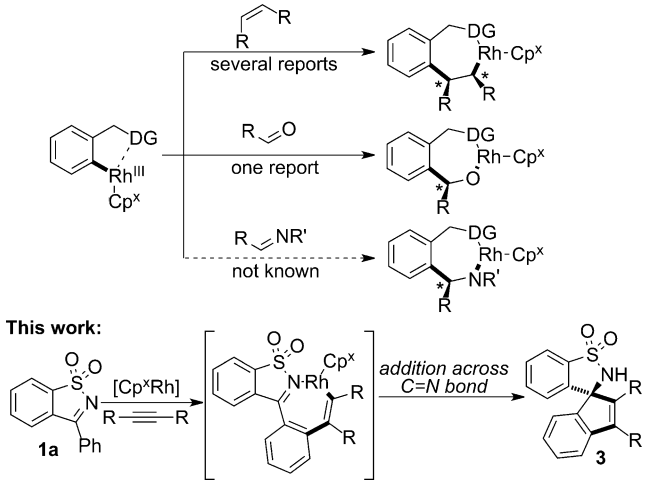


Figure 1. Spirocyclic sultams with relevant biological properties.

C–H functionalizations have emerged as a powerful strategy to access versatile building blocks from simple starting materials.[12,13] In this context, myriad transformations catalyzed by [Cp*Rh^{III}] complexes have been reported over the past few years.[14,15] Recently, the development of chiral cyclopentadienyl ligands[16] provided the requisite tools to embark on the development of asymmetric variants. In this regard, applications of chiral cyclopentadienyl ligands (Cp^x) in asymmetric catalysis have been devised.[17] By and large, the enantiodetermining step of the Rh^{III}-catalyzed transformation consisted of selective addition across an olefin.[16,17j] Despite their great utility, corresponding enantioselective additions across carbonyls[17f] or imines remain underexplored.[18] The Rh^{III}-catalyzed annulation reported by Deng and co-workers[9d] represents an opportunity to investigate the required catalyst properties and the feasibility of such additions. Herein, we report an enantioselective access to spirocyclic sultams **3** from *N*-sulfonyl ketimines **1** and alkynes using a chiral [Cp^{x}Rh^{III}]-catalyzed [3+2] annulation reaction (Scheme 1).

We initially explored this transformation with two chiral [Cp^{x}Rh^I] complex families, using *N*-sulfonyl ketimine **1a** and diphenyl acetylene **2a** as substrates (Table 1). The well soluble $Cu(OPiv)_2$ was used as oxidant to generate the chiral [Cp^{x}Rh^{III}] catalyst in situ. Both Cp families afforded the desired product in excellent yield at ambient temperature (Table 1, entries 1 and 2). Complex **Rh2**, with an atropchiral biaryl ligand scaffold, afforded a better enantioselectivity (Table 1, entry 2). Bulkier *ortho* substituents on the biaryl portion of the ligand (R = O*i*Pr



Scheme 1. Enantioselective additions of [ArRh^{III}] species across C=C, C=O, and C=N acceptors.

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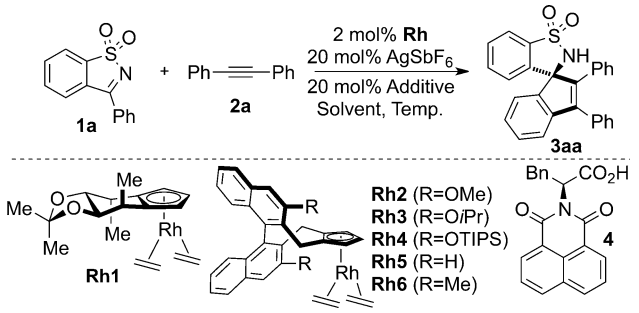
Table 1. Optimization of Enantioselective Spirocyclic Sultam Synthesis.[a]



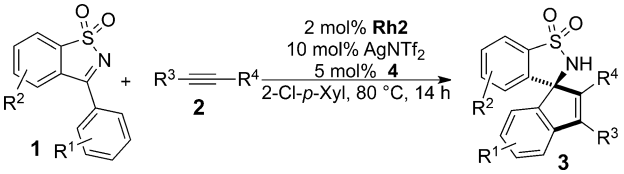
Entry	Rh	Additive	Solvent	T [°C]	Yield [%][b]	e.r.[c]
1	**Rh1**	$Cu(OPiv)_2$	DCE	30	99	61:39
2	**Rh2**	$Cu(OPiv)_2$	DCE	30	99	84.5:15.5
3	**Rh3**	$Cu(OPiv)_2$	DCE	30	99	77.5:22.5
4	**Rh4**	$Cu(OPiv)_2$	DCE	30	90	47:53
5	**Rh5**	$Cu(OPiv)_2$	DCE	30	19	60.5:39.5
6	**Rh6**	$Cu(OPiv)_2$	DCE	30	52	66:34
7	**Rh2**	$Cu(OPiv)_2$	DCE	80	99	86:14
8	**Rh2**	$Cu(OPiv)_2$	PhCl	80	99	90:10
9[d]	**Rh2**	PivOH	Cl-*p*-Xyl	80	81	92.5:7.5
10[d]	**Rh2**	AcOH	Cl-*p*-Xyl	80	81	91:9
11[e]	**Rh2**	**4**	Cl-*p*-Xyl	80	99	93:7
12[f]	**Rh2**	**4**	Cl-*p*-Xyl	80	99	92.5:7.5
13[e]	**Rh2**	*ent*-**4**	Cl-*p*-Xyl	80	99	93:7
14[g]	**Rh2**	**4**	Cl-*p*-Xyl	80	0	–
15[h]	**Rh2**	–	Cl-*p*-Xyl	80	19	89:11

[a] Conditions (unless otherwise stated): **1a** (0.05 mmol), **2a** (0.06 mmol), **Rh** (1.00 μmol), $AgSbF_6$ (10.0 μmol), 0.10 M solution in solvent, 18 h; [b] isolated product; [c] determined by HPLC with a chiral stationary phase; [d] 10 mol% $AgSbF_6$, 5 mol% additive, 2 h; [e] 10 mol% $AgNTf_2$ instead of $AgSbF_6$, 5 mol% additive, 2 h; [f] 1 mmol scale and 10 mol% $AgNTf_2$; [g] 5 mol% **4**, no $AgSbF_6$, 2 h; [h] 10 mol% $AgSbF_6$, 2 h.

or OTIPS; Table 1, entries 3 and 4), as well as smaller groups (R = H or Me; entries 5 and 6), decreased the enantioselectivity. In addition, the smaller ligands displayed significantly reduced reactivity. A higher reaction temperature resulted in better enantioselectivity (Table 1, entry 7). This behavior may be attributed to enhanced equilibration rate between conformations. Solvent screening revealed that chlorinated aromatic solvents were beneficial. For instance, chlorobenzene gave **3aa** in virtually quantitative yields with 90:10 e.r. (Table 1, entry 8). Combining $AgSbF_6$ and a simple carboxylic acid (PivOH or AcOH) in 2-chloro-*p*-xylene solvent resulted in enhanced reactivity, giving **3aa** in good yield and improved enantioselectivity in a shorter reaction time of 2 h (Table 1, entries 9 and 10). Using protected L-phenylalanine (**4**) and $AgNTf_2$ further enhanced the reactivity while maintaining a very good level of enantioselectivity (Table 1, entry 11), which was retained when the reaction was carried out on a larger scale (entry 12). Notably, the chirality of the additive **4** proved to be irrelevant as *ent*-**4** provided identical selectivity (Table 1, entry 13). Omitting the silver oxidant shut down the reactivity completely, and in the absence of a carboxylic acid, poor yields of **3aa** were observed (Table 1, entries 14 and 15).

Under the aforementioned optimized conditions, the scope of the cyclization was investigated (Table 2). The reaction proved to be compatible with different substituents at the *para* position of the ketimine-aryl ring. For instance, both electron-rich and electron-poor substituents were well tolerated and the respective spirocyclic sultams were obtained in good to excellent yields and high enantioselectivities (Table 2, entries 1–7). Notably, several synthetically valuable functional

Table 2. Enantioselective spirosultam synthesis.[a]



Entry	3		Yield [%][b]	e.r.[c]
1[d]	**3ba** (R^1 = OCF_3)		99	95.5:4.5
2	**3ca** (R^1 = OTf)		70	94.5:5.5
3	**3da** (R^1 = OMe)		71	94.5:5.5
4[d]	**3ea** (R^1 = CF_3)		99	96:4
5	**3fa** (R^1 = F)		88	94:6
6	**3ga** (R^1 = Ac)		91	95.5:4.5
7	**3ha** (R^1 = CHO)		99	95:5
8	**3ia**		65	90:10
9[d]	**3ja**		99	95:5
10	**3ka**		99	94:6
11	**3la**		50	88:12
12	**3eb** (R^3 = R^4 = *p*-ClPh)		86	97:3
13	**3ec** (R^3 = R^4 = *p*-F_3CPh)		70	97:3
14	**3ed** (R^3 = R^4 = 3,5-Xyl)		99	96:4
15	**3ee** (R^3 = R^4 = 2-Np)		99	97:3
16	**3ef** (R^3 = Ph, R^4 = 2-Np)		60	96:4
	3ef′ (R^3 = 2-Np, R^4 = Ph)		40	97:3
17	**3eg** (R^3 = PMP, R^4 = *p*-F_3CPh)		66	94:6
	3eg′ (R^3 = *p*-F_3CPh, R^4 = PMP)		33	96.5:3.5
18	**3eh** (R^3 = CO_2Me, R^4 = Ph)		71	87.5:12.5
	3eh′ (R^3 = Ph, R^4 = CO_2Me)		28	88.5:11.5
19	**3ei** (R^3 = Me, R^4 = Ph)		70	70:30
	3ei′ (R^3 = Ph, R^4 = Me)		29	90.5:9.5
20	**3ej** (R^3 = R^4 = Bu)		49	68:32

[a] Conditions (unless otherwise stated): **1** (0.05 mmol), **2** (0.06 mmol), **Rh2** (1.00 μmol), $AgNTf_2$ (5.00 μmol), **4** (2.50 μmol), 0.10 M in 2-chloro-*p*-xylene, 80 °C, 14 h; [b] isolated product; [c] determined by HPLC with a chiral stationary phase; [d] 1 mmol scale.

groups, such as a triflate, aldehyde, or ketone are well tolerated in this process (Table 2, entries 2, 6, and 7). A *m*-CF_3 group led to slightly reduced yield and selectivity (Table 2, entry 8), whereas a 2-naphthyl moiety had no detrimental effect on the selectivity (entry 9). Substitution (*p*-Cl) on the arenesulfonyl core is also possible (Table 2, entry 10). Besides the cyclic *N*-sulfonyl ketimines, a cyclic sulfamidate substrate could be used, affording spirocyclic product **3la** (Table 2, entry 11). We next evaluated the influence of different alkynes in this transformation. Aryl alkynes with different electronic and steric properties were excellent coupling partners, delivering the chiral spirocyclic sultams in high enantioselectivities (Table 2, entries 12–15). Although unsymmetrical aryl alkynes reacted with weak regioselectivities, excellent enantioselectivities were maintained (Table 2, entries 16 and 17). Alkynes with a single aryl substituent reacted well, albeit with moderate regioselectivities and enantioselectivities depending on the substituent and the regioisomer (Table 2, entries 18 and 19). A dialkyl alkyne displayed reduced reactivity and selectivity (entry 20).

The absolute configuration of the sultams were unambiguously established by X-ray crystallographic analysis of **3ja** to be *R* (Figure 2).

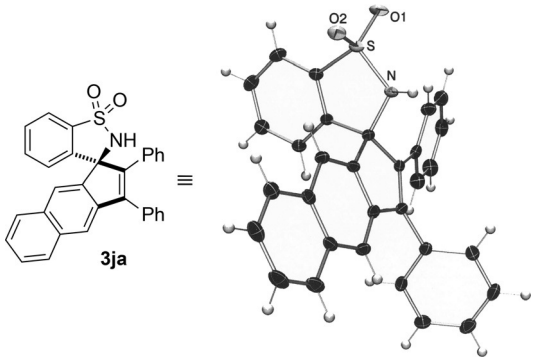
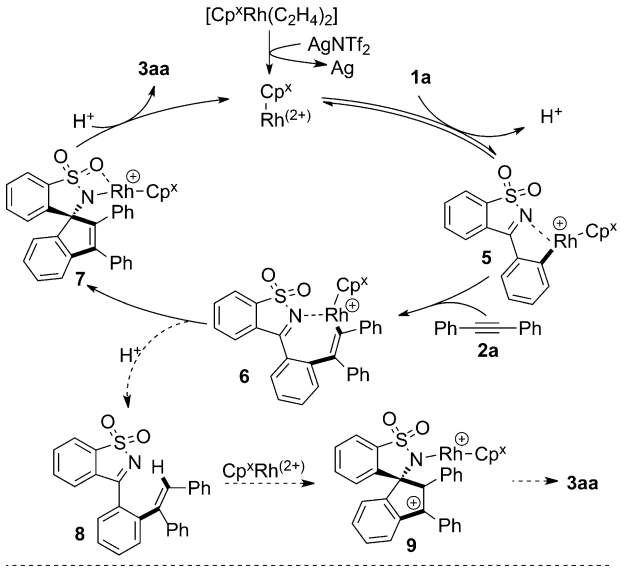


Figure 2. X-ray crystal structure and absolute configuration of sultam **3ja**.

The following mechanistic scenario is plausible for this transformation (Scheme 2). Oxidation of the [Cp^xRh^I] complex by the silver salt generates a cationic [Cp^xRh^{III}] species.[19] The carboxylic acid additive should give a monocationic species. C–H activation directed by the *N*-sulfonyl imino group gives cyclometalated compound **5**.[20] Association of alkyne **2** and migratory insertion would lead to intermediate **6**. The subsequent enantiodetermining addition across the C=N bond would set the spirocyclic stereocenter of **7**. Finally, protonation would deliver product **3** and closes the catalytic cycle. An alternative reaction pathway could be envisioned involving first a hydroarylation of **1a** giving alkene **8**. A subsequent asymmetric Friedel-Crafts cyclization[21] with [Cp^xRh^{III}] bound to the imine could yield **9** and then product **3aa**.[9b] Exposure of independently prepared intermediate **8** to the reaction conditions gave sultam **3aa** in completely racemic fashion, indicating that this pathway is less likely. $AgSbF_6$ alone was able to induce cyclization, whereas $AgNTf_2$ proved to be inert.



8 → 3aa — Conditions: Cl-*p*-xylene, 80 °C, 2 h

Rh2 [%]	$AgNTf_2$ [%]	4 [%]	Yield [%]	e.r.
2.5	4.5	5	99	50:50
-	10	-	0	-
-	10*	-	85	50:50
-	-	10	0	-
10	-	-	0	-

* $AgSbF_6$

Scheme 2. Proposed mechanism for enantioselective spirocycle formation and controls.

In conclusion, we have reported a chiral Cp^x–rhodium(III)-catalyzed synthesis of spirocyclic indenyl sultams by enantioselective annulation of *N*-sulfonyl ketimines and alkynes. The enantiodetermining addition across the imine is shown to be influenced by the chiral Cp^x ligand, as well as a judicious choice of carboxylic acid additives. The spirocyclic sultams were obtained in high yields and enantiomeric ratios and their relevance renders this method attractive for synthetic and medicinal chemistry. Moreover, this study further adds to the generality of the chiral cyclopentadienyls based on an atropchiral biaryl backbone as a versatile chiral ligand class.

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Keywords: asymmetric catalysis · C–H activation · chiral Cp ligands · rhodium · sultams

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