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Spirocyclic Sultam and Heterobiaryl Synthesis through Rh-Catalyzed Cross-Dehydrogenative Coupling of *N*-Sulfonyl Ketimines and Thiophenes or Furans

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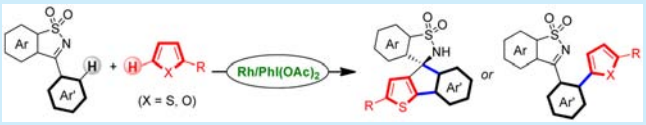
Supporting Information

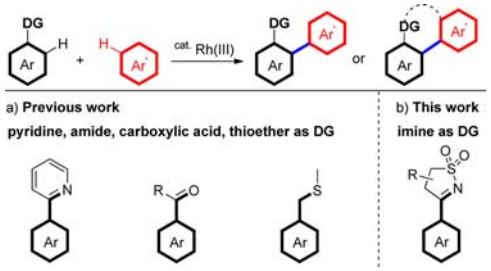
ABSTRACT: A useful approach is developed for the synthesis of various structurally interesting spirocyclic sultams and heterobiaryls using a cross-dehydrogenative coupling strategy that features high atom and step economy. This method employs $[Cp^*RhCl_2]_2$ as a catalyst and *N*-sulfonylimine, a weak coordinating group, as an efficient directing group to assist C−H activation. A number of the coupled products were converted into interesting molecules through further synthetic transformations.



Owing to atom economy and step efficiency, the cross-dehydrogenative coupling (CDC) represents a highly important synthetic strategy for the construction of a valuable biaryl scaffold[1] that is ubiquitous in a large number of molecules, such as pharmaceuticals, agrochemicals, and functional materials.[2] Despite the significance of CDC toward biaryls, one of the great challenges posed by this synthetic method is controlling reaction chemoselectivity to avoid the undesired homocoupling byproducts. To this end, a few protocols have been developed, including the utilization of an excess of arenes[3] and two electronically distinctly different substrates.[4,5] Another useful and commonly used strategy is the use of coordinating functionalities as directing groups, which not only can improve both the chemoselectivity and regioselectivity of the CDC but also may provide a platform for the construction of structurally interesting compounds by means of further synthetic transformations.[6] In this respect, pyridine, amide, and carbamate groups have shown good reactivity. In spite of these advances, the scope remains relatively narrow. Therefore, it is highly desirable to exploit a wide range of arenes to the CDC for the rapid construction of biaryls and related compounds.

Rhodium(III) complexes, $[Cp^*RhCl_2]_2$ in particular, have received increasing attention in C−H functionalization because of their high catalytic efficiency and good functional group compatibility.[7] Many reports have demonstrated their potential in oxidative Heck reactions[8] and C−H additions to unsaturated bonds.[9] In sharp contrast, the Rh(III)-catalyzed cross-dehydrogenative arylation remains underdeveloped.[10] Glorius recently reported an elegant CDC protocol which revealed that arenes bearing an amide functionality can be coupled with halogen-substituted benzenes in the presence of $[Cp^*RhCl_2]_2$.[10a] Since then, pyridine,[10c] carboxylic acid,[10f−h] and thioether[10e] were also explored for the Rh(III)-catalyzed cross-dehydrogenative arylation. However, the type of the directing groups remains rather narrow (Scheme 1a).

Scheme 1. Rh(III)-Catalyzed Cross-Dehydrogenative Arylation with the Assistance of Directing Groups



Imines are not only useful reagents in a wide variety of organic transformations but are also versatile ligands in organometallics.[11] As such, the imine-assisted C−H functionalization is highly significant to synthetic and organometallic chemists. Although imines have been used in some C−H functionalizations,[12] there is no example, to the best of our knowledge, of the cross-dehydrogenative arylation directed by the imine group. As a consequence, we became interested in exploiting the imine functionality as a directing group in cross-dehydrogenative arylation for the biaryl synthesis. Herein, we disclose a Rh(III)-catalyzed approach for the rapid assembly of an array of spirocyclic sultams and heterobiaryls through cross-dehydrogenative heteroarylation of *N*-sulfonyl ketimines with thiophenes or furans (Scheme 1b). In the reactions, *N*-sulfonyl imine, a weak coordinating group, acts as an efficient directing group to assist C−H cleavage. Note that such a C−H/C−H coupling method is an extremely rare example for the construction of structurally interesting yet synthetically challenging spirocyclic sultams that have potential synthetic usefulness and biological activities.[13]

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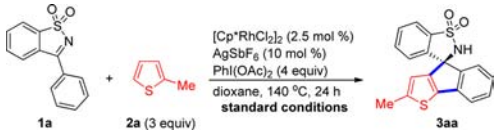
We commenced our studies by investigating the reaction between *N*-sulfonylketimine **1a** and 2-methylthiophene **2a** with $[Cp^*RhCl_2]_2$ as the catalyst. The coupling reaction did not afford the expected biaryl product but instead resulted in an interesting spirocyclic sultam. After systematically examining the reaction parameters, we identified an effective catalytic system containing $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $PhI(OAc)_2$ (4 equiv), which enable the coupling reaction to take place at 140 °C in dioxane to furnish the spirocyclic sultam **3aa** in 82% yield (entry 1, Table 1). Some key results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions[a]



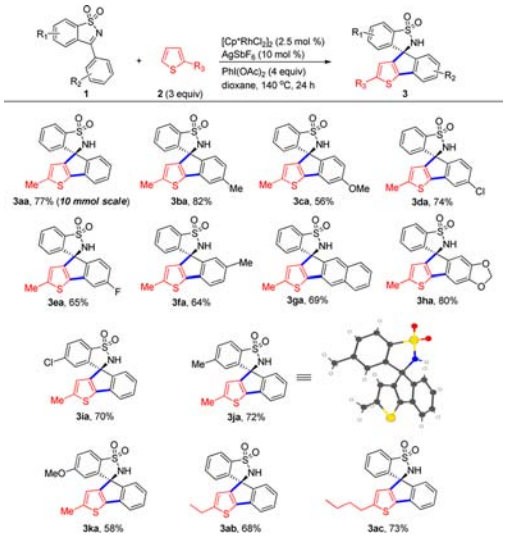
entry	change from the standard conditions	conv of **1a**[b] (%)	yield[b] (%)
1	no change	85	83 (82)[c]
2	without $AgSbF_6$	5	trace
3	2 equiv of $Cu(OAc)_2$ or Ag_2CO_3 instead of $PhI(OAc)_2$	0	0
4	2 equiv of $K_2S_2O_8$ instead of $PhI(OAc)_2$	18	16
5	2 equiv of $PhI(OAc)_2$ used	57	56
6	120 °C instead of 140 °C	67	66
7	addition of 1 equiv of K_2CO_3	33	31
8	addition of 1 equiv of NaOAc	2	trace
9	addition of 1 equiv of PhCOOH	57	56
10	addition of 1 equiv of HOAc	49	48
11	toluene instead of dioxane	18	16
12	DME instead of dioxane	36	34
13	DCE, *t*-AmylOH, MeCN or DMSO instead of dioxane	0	0

[a]Reactions were performed on a 0.2 mmol scale. [b]Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield.

The use of $AgSbF_6$ is crucial to the transformation since only a trace amount of **3aa** was observed without such additive (entry 2). The commonly used oxidants in the Rh(III) catalysis, $Cu(OAc)_2$, and Ag_2CO_3 were totally not effective, and the ketimine **1a** was recovered (entry 3). The reaction only gave rise to **3aa** in 16% yield in the presence of 2 equiv of $K_2S_2O_8$ (entry 4). In addition, reducing the amount of $PhI(OAc)_2$ from 4 to 2 equiv and lowering the temperature from 140 to 120 °C led to 56 and 66% yields, respectively (entries 5 and 6). The addition of inorganic base or carboxylic acid, such as K_2CO_3, NaOAc, PhCOOH, and HOAc, all exhibited negative results (entries 7−10). A screening of other solvents indicated that the reaction occurred sluggishly in toluene and DME (entries 11and 12) and did not take place in DCE, *t*-AmylOH, MeCN, and DMSO (entry 13).

Under the optimized reaction conditions, we next explored the substrate scope of Rh(III)-catalyzed CDC for the synthesis of various spirocyclic sultams (Scheme 2).[14] The *N*-sulfonylketimines bearing electron-donating and -withdrawing groups on the ketimine aryl ring displayed good reactivity, providing the corresponding products in 56−82% yields (**3ba**−**ea**). In the case of a substrate bearing a methyl substituent at the *meta*-position of the ketimine aryl ring, C−C bond formation took place exclusively at the less hindered site (**3fa**). In addition, naphthalene- and 3,4-(methylenedioxy)benzene-derived ketimines also reacted with **2a** to produce the target products **3ga** and **3ha** in 69 and 80% yields, respectively. Unfortunately, the sterically hindered *o*-methyl-substituted ketimine was unreactive. Furthermore, ketimines with methyl, chloro, and methoxy groups on the isothiazole ring were also examined. The reactions occurred smoothly to furnish the desired products in moderate to good yields (**3ia**−**ka**). The structure of **3ja** was unambiguously confirmed by single-crystal X-ray diffraction.[15] In addition, 2-ethylthiophene and 2-butylthiophene were also suitable for the reactions, giving rise to **3ab** and **3ac** in 68 and 73% yields, respectively. Note that this method is suitable for gram scale, which was demonstrated by a 10 mmol scale reaction between **1a** and **2a**.

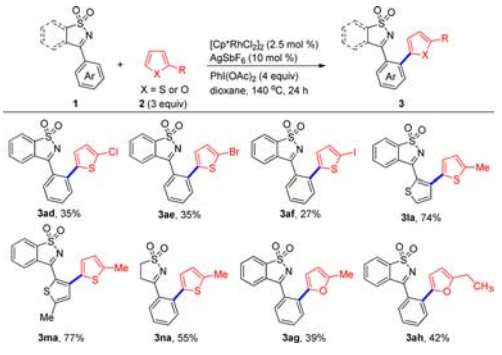
Scheme 2. Rh-Catalyzed Spirocyclic Sultam Synthesis[a]



[a]Reactions were performed on a 0.2 mmol scale. Isolated yields are indicated.

During the course of our investigation of the substrate scope with regard to thiophenes, we were surprised to find that the thiophenes with an electron-withdrawing group, such as chloro, bromo, and iodo, reacted with **1a** to generate the corresponding heterobiaryls instead of spirocyclic sultams (**3ad**−**af**, Scheme 3). Additionally, the heteroarylated products were also observed in the coupling reactions between thiophene-derived ketimines and **2a**, which delivered **3la** and **3ma** in 74 and 77% yields, respectively. Besides ketimines derived from saccharins, cyclic

Scheme 3. Rh-Catalyzed Biaryl Synthesis[a]



[a]Reactions were performed on a 0.2 mmol scale. Isolated yields are indicated.

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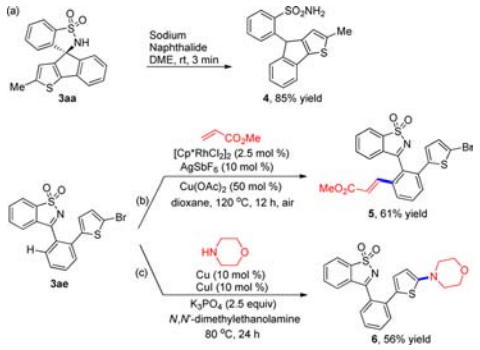
ketimine **1n** was also a suitable substrate in the C−H heteroarylation reaction, producing **3na** in 55% yield. The reaction was also amenable to furan derivatives. Thus, the corresponding biaryls were formed in synthetically useful yields for 2-methylfuran and 2-ethylfuran (**3ag** and **3ah**). Unfortunately, thiophenes and furans with substituents on the C3 position were unreactive.

The usefulness of the products obtained in the Rh(III)-catalyzed cross-dehydrogenative coupling was demonstrated by the following synthetic transformations (Scheme 4). The

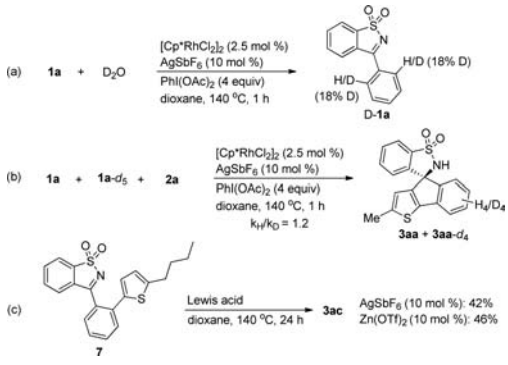
Scheme 4. Synthetic Transformations



spirocyclic sultam **3aa** was rapidly converted into sulfonamide **4** in good yield with sodium naphthalide (Scheme 4a). In addition, a bis-substituted *N*-sulfonylketimine **5** was generated in 61% yield using C−H olefination method developed by our group (Scheme 4b).[8j] Moreover, the tolerance of bromo functionality provides us an opportunity to construct C−N bond. Thus, a morpholine-containing biaryl was obtained through Cu-catalyzed cross-coupling reaction (Scheme 4c).[16]

To gain more insight into the reaction mechanism, several experiments were conducted (Scheme 5). First, an H/D

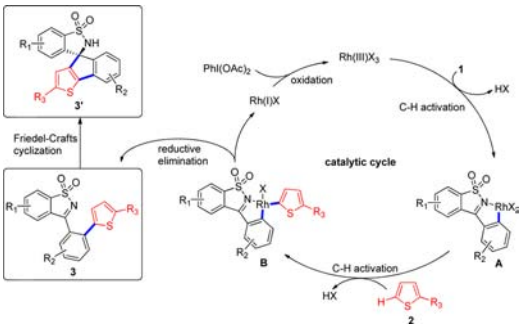
Scheme 5. Mechanistic Studies



exchange experiment between **1a** and 10 equiv of D_2O suggested that a reversible C−H cleavage was involved in the reaction because 18% D was introduced into the two *ortho* positions of the ketimine aryl ring (Scheme 5a). Second, an intramolecular competition reaction between **1a** and **1a**-d_5 showed a KIE of 1.2, illustrating that the rate-limiting step does not involve the C−H cleavage (Scheme 5b).[17] Third, a biaryl compound **7** was converted into the spirocyclic sultam **3ac** in the presence of Lewis acid, such as $AgSbF_6$ and $Zn(OTf)_2$ (Scheme 5c). As such, Lewis acid-mediated Friedel−Crafts type cyclization might be involved in the transformation of biaryl compounds into spirocyclic sultams.

On the basis of our preliminary mechanistic studies, we suggest a possible catalytic cycle to involve an initial formation a five-membered rhodacycle species **A** by chelation-assisted C−H activation (Scheme 6).[18] This complex then reacts with

Scheme 6. Hypothesis for Rh-Catalyzed Spirocyclic Sultam and Biaryl Synthesis



thiophene **2** to deliver an intermediate **B** by C−H activation once again. Subsequently, the species **B** occurs reductive elimination to produce biaryl product **3** and a low-valent Rh(I) complex. The latter is finally oxidized into Rh(III) catalyst with the aid of $PhI(OAc)_2$ to fulfill the catalytic cycle. Depending on the structural and electronic property, **3** could be converted into spirocyclic sultam **3′** through Friedel−Crafts-type cyclization.

In summary, we have realized a Rh(III)-catalyzed cross-dehydrogenative coupling method to prepare various structurally interesting and synthetically useful spirocyclic sultams and heterobiaryls from readily accessible *N*-sulfonylketimines and thiophenes or furans. In the reactions, the *N*-sulfonylimine functionality is employed as an effective directing group for C−H activation. Our ongoing studies focus on the use of the CDC strategy to construct additional heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00197.

Detailed experimental procedures, characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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