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Highly Functionalized Pyridines Synthesis from *N*-Sulfonyl Ketimines and Alkynes Using the N−S Bond as an Internal Oxidant

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Supporting Information

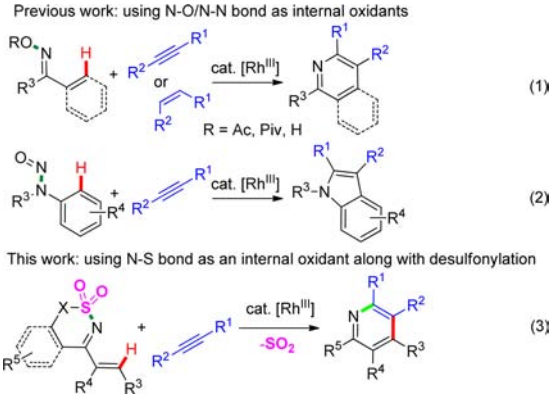
ABSTRACT: The N−S bond-based internal oxidant offers a distinct approach for the synthesis of highly functionalized pyridines. A novel Rh(III)-catalyzed one-pot process undergoes an efficient C−C/C−N bond formation along with desulfonylation under very mild conditions. The method is quite simple, general, and efficient.

Highly functionalized pyridines represent an important class of hererocycles that are widely implicated in natural products, functional materials, and medicinal chemistry.[1] While methods for the synthesis of this motif have been developed over the past several decades,[2,3] there is increased interest in this field due to the continued importance of the pyridine core in various fields. Thus, the development of new approaches to pyridines is highly desirable.

Transition-metal-catalyzed C−H activation has been realized as an efficient strategy for synthesis of heterocyclic scaffolds.[4] Recently, a number of approaches were well studied where C−H activation with internal oxidants prepared nitrogen-containing heterocycles.[5−8] For example, isoquinoline and pyridine synthesis from α,β-unsaturated oximes and internal alkynes/alkenes were demonstrated via Rh(III)-catalyzed transformation, in which the N−O bond of the oxime acts as an internal oxidant (Scheme 1, approach 1).[6] In a recent report Zhu demonstrated that the N−N bond-based internal oxidant approach offers indole synthesis (Scheme 1, approach 2).[8]

Despite this progress, however, restricted internal oxidant protocols have been utilized for C−N cyclization. Especially, to the best of our knowledge, N−S bonds have not been reported to function as internal oxidants in C−H activation protocols. In addition, more reactive electrophiles such as cyclic *N*-sulfonylimines have rarely been developed as directing groups for pyridines synthesis by C−N bond formation along with desulfonylation.[9−12] Herein, we report a novel approach which comprises Rh(III)-catalyzed C−H activation of simple *N*-sulfonyl ketimines and internal alkynes to afford the highly functionalized pyridines, where the N−S bond could work as an internal oxidant (Scheme 1, approach 3). The one-pot process undergoes an efficient C−N bond formation and concomitant desulfonylation under very mild conditions.

Scheme 1. Rhodium(III)-Catalyzed C−H Activation with Internal Oxidants



We commenced our investigation by studying the coupling of cyclic *N*-sulfonyl ketimine **1a** with diphenyl acetylene **2a** (Table 1). Using $[Cp^*RhCl_2]_2$ as a catalyst, $Cu(OAc)_2$ did work, but **3aa** was formed in only a low yield (Table 1, entry 1). Meanwhile, among various silver salts, CF_3SO_3Ag and $AgBF_4$ provided better yields (Table 1, entries 2−5). Additional solvents were screened for the reaction, in which HOAc exhibited good reactivity and improved the yield to 45% (Table 1, entries 6−9). To our surprise, the reaction can be carried out with excellent efficiency in the presence of HOAc in DCE (Table 1, entries 10 and 11). Among the study of other acids, CF_3COOH and pivalic acid were also appropriate for the reaction and gave **3aa** in 64% and 79% yields, respectively (Table 1, entries 12 and 13). In addition, the lower catalyst loading still gave a good yield even when the temperature was reduced to only 60 °C (Table 1, entries 14 and 15). Indeed, when the amount of diphenyl acetylene **2a** was lowered to 1.2 equiv, a good yield of **3aa** was achieved (Table 1, entry 16). To our delight, the reactivity was still excellent even when the $AgBF_4$ was lowered to 0.5 equiv; however, 0.3 equiv of $AgBF_4$ gave rise to a lower yield (Table 1, entries 17 and 18). This suggests that the N−S bond supports its role as an internal

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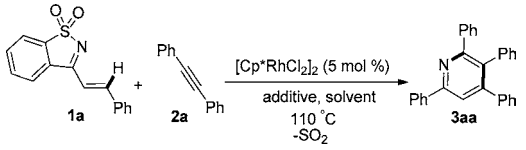
Table 1. Optimization of the Reaction Conditions for Synthesis of 3aa[a]



entry	additive	acid [equiv]	solvent	t (h)	yield (%)[b]
1	$Cu(OAc)_2$	–	DCE	46	16
2	$AgSbF_6$	–	DCE	46	mess
3	CF_3SO_3Ag	–	DCE	46	31
4	CH_3CO_2Ag	–	DCE	46	9
5	$AgBF_4$	–	DCE	46	32
6	$AgBF_4$	–	DMF	46	trace
7	$AgBF_4$	–	THF	46	20
8	$AgBF_4$	–	^{t}BuOH	23	27
9	$AgBF_4$	–	HOAc	12	45
10	$AgBF_4$	HOAc/2	DCE	12	73
11	$AgBF_4$	HOAc/5	DCE	12	80
12	$AgBF_4$	CF_3CO_2H/5	DCE	12	64
13	$AgBF_4$	pivalic acid/5	DCE	12	79
14[c]	$AgBF_4$	HOAc/5	DCE	12	87
15[c,d]	$AgBF_4$	HOAc/5	DCE	12	87
16[c,d,e]	$AgBF_4$	HOAc/5	DCE	12	86
17[c,d,e,f]	$AgBF_4$	HOAc/5	DCE	12	**85**
18[c,d,e,g]	$AgBF_4$	HOAc/5	DCE	12	65

[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 0.2 mmol of **2a**, 5 mol % of $[Cp^*RhCl_2]_2$, 1.0 equiv of additive, 1 mL of solvent, 110 °C, Ar atmosphere. [b]Isolated yield. [c]2.5 mol % of $[Cp^*RhCl_2]_2$. [d]60 °C. [e]0.1 mmol of **1a**, 0.12 mmol of **2a**. [f]50 mol % of $AgBF_4$. [g]30 mol % of $AgBF_4$.

oxidant in the catalytic cycle. The structure of the final product **3aa** was characterized by X-ray crystallography (Figure 1).[13,14]

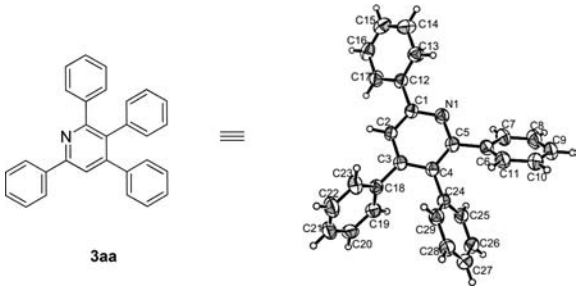
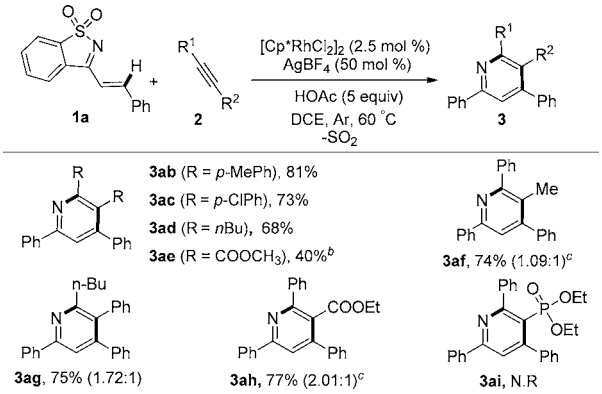


Figure 1. X-ray crystal structure of **3aa**.

Utilizing optimal reaction conditions, various alkynes were studied with *N*-sulfonyl ketimine **1a** (Table 2). The process showed wide substrate tolerance with internal alkynes. With substituted diaryl acetylenes even for an alkyl-disubstituted alkyne, the corresponding products can be obtained in good yields (**3ab**–**3ad**). However, with electron-deficient **2e** as the internal alkyne, the desired product **3ae** was obtained in a low yield. To study the regioselectivity of this reaction, a few disubstituted unsymmetrical alkynes were employed to give the isomers in good yields with poor regioselectivity (**3af**–**3ah**), whereas no product was obtained when **2i** was employed.

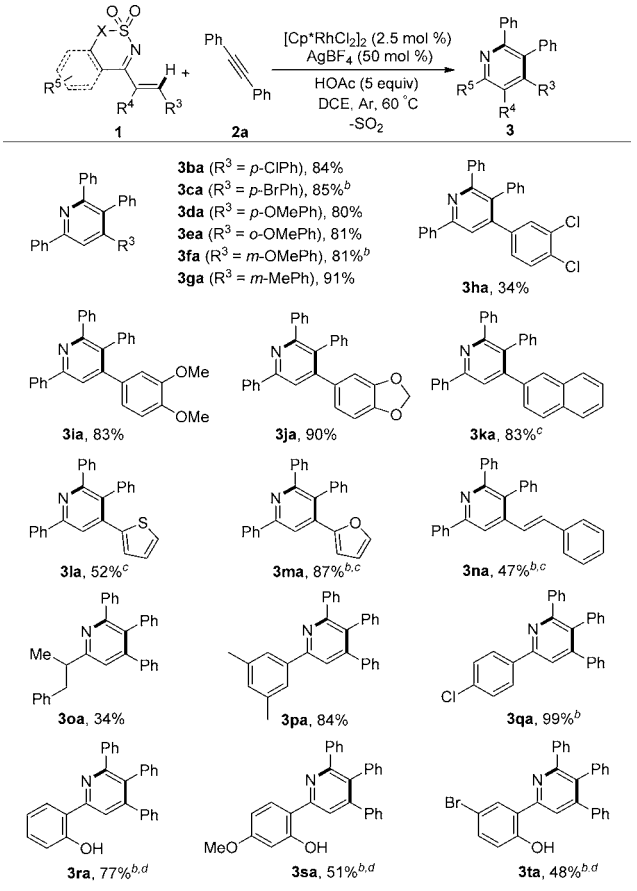
Subsequently, a range of substituted cyclic *N*-sulfonyl ketimines **1** were employed and the corresponding pyridine derivatives were constructed effectively (Table 3). The *β*-

Table 2. Substrate Scope of Alkynes[a]



[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 0.12 mmol of **2**, 2.5 mol % of $[Cp^*RhCl_2]_2$, 50 mol % of $AgBF_4$, 0.5 mmol of HOAc, 1 mL of DCE, 60 °C, Ar atmosphere. Yields are reported for the isolated products. Ratios of regioisomers are given within parentheses and were determined by ^{1}H NMR analysis. Major isomers are shown. [b]0.5 mL of HOAc, 0.5 mL of DCE. [c]1.0 equiv of $AgBF_4$.

Table 3. Substrate Scope and Limitations of *N*-Sulfonyl Ketimines Patterns[a]



[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1**, 0.12 mmol of **2a**, 2.5 mol % of $[Cp^*RhCl_2]_2$, 50 mol % of $AgBF_4$, 0.5 mmol of HOAc, 1 mL of DCE, 60 °C, Ar atmosphere. Yields are reported for the isolated products. [b]1.0 equiv of $AgBF_4$. [c]0.12 mmol of **1**, 0.1 mmol of **2a**, 0.5 mL of HOAc, 0.5 mL of DCE. [d]5 mol % of $[Cp^*RhCl_2]_2$, 0.5 mL of HOAc, 0.5 mL of DCE.

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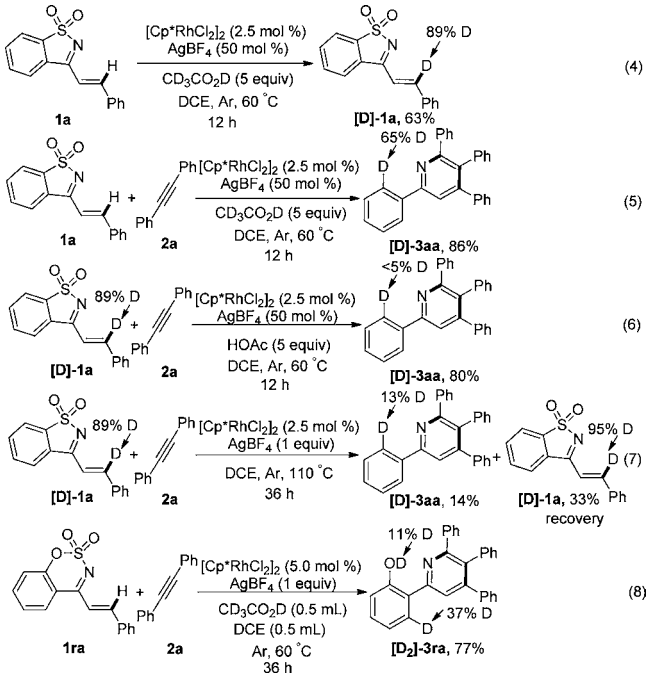
position of the olefin unit bearing electron-withdrawing substituents at the *para*-position of the aryl ring gave the products in good yields (**3ba**, **3ca**). In addition, a methoxy at the *para*-, *meta*-, or *ortho*-position could react smoothly to afford the products with good yields (**3da**−**3fa**). Similarly, **1g** also provided the product **3ga** in 91% yield. However, a 3,4-dicholoro-substituted substrate only produced the corresponding pyridine **3ha** in 34% yield, probably because of the electrical effect. Moreover, other 3,4-disubstituted aryl substrates **1i**−**1k** proceeded smoothly to produce the product in good yields (**3ia**−**3ka**).

Fortunately, *N*-sulfonyl ketimines bearing heteroaryl groups were also compatible, producing **3la** and **3ma** in 52% and 87% yields, respectively. The conjugated diene aryl substituent gave **3na** in only 47% yield with some side reactions. Notably, the 6-pyridine alkenyl derivative **3oa** could be prepared in 34% yield in this reaction.[14] Importantly, *N*-sulfonyl ketimines fused with an array of diversely substituted benzene rings were also tolerated under the standard conditions, furnishing the pyridines in good to excellent yields (**3pa**, **3qa**). Encouraged by the good tolerance toward various functional groups, the scope of six-membered ring benzo-fused imines **1r**−**1t** was further examined. Surprisingly, the Rh catalyst was also effective for these various imines to generate the expected pyridines which contain the phenolic hydroxyl group (**3ra**−**3ta**).

To investigate the mechanism of this reaction, deuterium-labeling experiments were carried out (Scheme 2). When **1a**

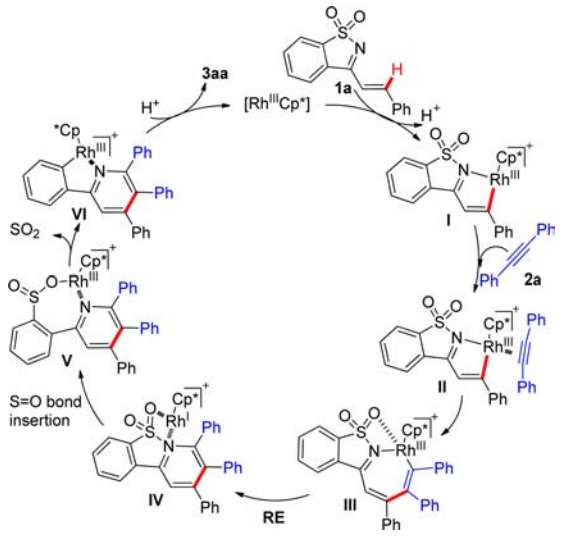
Scheme 2. Deuterium-Labeling Experiments



was conducted in CD_3CO_2D in the absence of alkynes, deuterium was observed at the *ortho*-position, which indicated the possibility of the reaction pathway via oxidative addition of an *ortho* C−H bond (eq 4). In contrast, the same reaction was conducted in the presence of **2a**, and the product **3aa** was observed with 65% deuterium (eq 5). Yet, when the reaction of isotopically labeled **1a** and **2a** was performed in CH_3CO_2H with standard conditions, no obvious deuterium content in product **3aa** was obtained (eq 6). Furthermore, the reaction without CH_3CO_2H gave **3aa** with a deuterium content of 13%, meanwhile the content of deuterium in the recovered **1a** was increased from 89% to 95% (eq 7). All of these data imply that the first step of C−H activation is reversible and the proton used for the protonolysis in the catalytic system can be either from the solvent HOAc or produced in the first C−H bond metalation step (eqs 5−7). In particular, when **1ra** was treated in CD_3CO_2D, deuterium at the 6-position of the phenyl group in **3ra** was observed in 37%, which indicates that the rhodacycle might exist at a later stage of the catalytic cycle (eq 8).[14]

A plausible mechanism for the reaction is proposed in Scheme 3. In the first step, the rhodium catalyst coordinates to

Scheme 3. A Plausible Mechanism



the imine nitrogen of cyclic *N*-sulfonyl ketimine **1a** and subsequent *ortho* C−H activation yields the five-membered rhodacycle **I** with loss of a proton. Then coordination of an alkyne to a rhodium species gives intermediate **II**. Subsequently, alkyne regioselective insertion provides an alkyne coordinating seven-membered ring intermediate **III**. Intermediate **III** reductive elimination would afford the transition state Rh(I) species **IV**, which could simultaneously undergo insertion of a S═O bond and cleavage of the N−S bond. During this step, Rh(I) species **IV** may be oxidized to give seven-membered Rh(III) species **V** at the same time S(VI) was reduced to S(IV), which suggests the N−S bond is acting as an internal oxidant. And then, a five-membered rhodacycle **VI** was formed by elimination of SO_2. Finally, protonolysis of the C−Rh bond of **VI** may occur to form **3aa** and regenerate the [Rh(III)Cp*] species.

In summary, this appears to be the first example of developing Rh(III)-catalyzed C−H activation with the N−S bond of *N*-sulfonyl ketimines acting as a distinct internal oxidant to synthesize highly functionalized pyridines. And importantly, the reaction is accomplished through new C−C/C−N bond formation, and S−N/S−C (or S−O) bond cleavage, along with desulfonylation under very mild conditions. Studies on the catalytic mechanism and the full potential of this methodology are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, structural proofs, and NMR spectra of the products. 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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(13) Crystallographic Data for **3aa**: CCDC 971996, C29H21N, M: 383.47, Space group: $P\bar{1}$, Cell: a = 10.4662(4) Å, b = 12.0700(4) Å, c = 17.9603 Å, α = 86.884(3)°, β = 74.944(4)°, γ = 78.309(3)°, Temperature: 290(2) K, calcd: 1.187 mg/mm^3.

(14) For more details, see the Supporting Information.