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Rhodium-Catalyzed Intermolecular Amidation of Arenes with Sulfonyl Azides via Chelation-Assisted C−H Bond Activation

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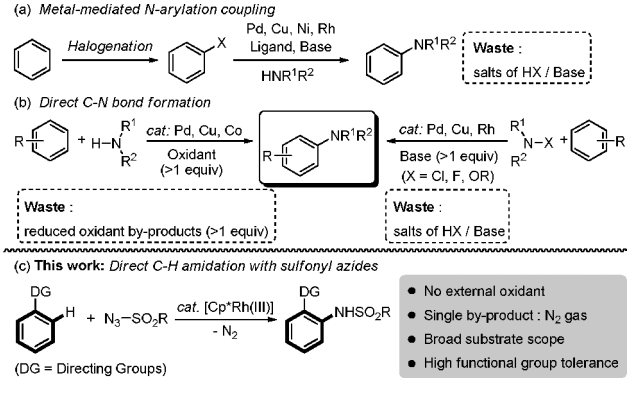
Supporting Information

ABSTRACT: We report the direct amidation of arene C−H bonds using sulfonyl azides as the amino source to release N_2 as the single byproduct. The reaction is catalyzed by a cationic rhodium complex under external oxidant-free conditions in the atmospheric environment. A broad range of chelate group-containing arenes are selectively amidated with excellent functional group tolerance, thus opening a new avenue to practical intermolecular C−N bond formation.

Aryl amines are a key component in numerous natural products and synthetic compounds displaying important chemical, biological, and medicinal properties.[1] As a result, there have long been extensive efforts toward the development of efficient reactions to introduce nitrogen-containing groups into arene molecules. Metal-mediated *N*-arylation of aryl (pseudo)halides with amines or amides has been developed as an attractive route to aminoarenes under various conditions, pioneered by Ullmann and Goldberg employing stoichiometric copper species.[2] Important advances in transition metal-catalyzed amination were made later, mainly by the Hartwig and Buchwald groups (Scheme 1a),[3] wherein palladium or copper catalysts were used in combination with suitable ligands under basic conditions.[4] However, this procedure generates stoichiometric amounts of byproducts such as hydrogen halides or their base salts. The development of a direct amination of arene C−H bonds is highly desirable.

Scheme 1. C−N Bond Formation Routes to Aryl Amines



In metal-catalyzed *direct C−H amination* of (hetero)arenes, two approaches can be conceived (Scheme 1b).[5] The first strategy is to use parent amines in the presence of external oxidants, and there are several examples reporting the direct amination of azoles,[6] polyfluorobenzenes,[6c] and chelate group-containing arenes.[7] An alternative strategy is to employ pre-activated amino precursors, which successfully led to the direct amination of various (hetero)arenes.[8,9] However, in these direct amination reactions employing arenes, generation of stoichiometric byproducts still cannot be avoided under the conditions used.[10]

These considerations led us to envision an environmentally benign direct C−H amidation of arenes that does not generate hazardous byproducts. In this context, we have successfully developed a Rh-catalyzed direct *N*-arylation using sulfonyl azides as an amino source and releasing N_2 as the single byproduct (Scheme 1c). Importantly, the chelation-assisted direct C−N amidation proceeds in the absence of external oxidants with high functional group tolerance. Although metal-catalyzed intramolecular sp^2 or sp^3 C−H amination was previously shown to annulate vinyl or aryl azides, giving rise to heterocycles,[11,12] azides have rarely been utilized for *intermolecular* reactions with arene C−H bonds. In fact, only limited examples are known wherein certain metal species catalyze *N*-atom transfer of aryl azides to the allylic or benzylic C−H bonds.[13]

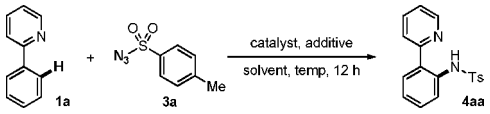
Based on previous observations that Rh(I),[14] Rh(II),[15] and Rh(III)[16] species are highly reactive in the oxidative C−H bond funtionalizations of arenes, we initially examined the prospective C−H amidation of 2-phenylpyridine (**1a**) with sulfonyl azides using available rhodium species (Table 1). Upon the extensive screening of reaction conditions,[17] we found that a cationic Rh(III) species, $[Cp^*Rh(III)](SbF_6)_2$, displayed a significant catalytic activity while other rhodium precursors were less effective (entries 1−5). Interestingly, this effect of cationic catalyst was especially dramatic with the $[RhCp^*Cl_2]_2$ complex, and the cationic rhodium species were readily prepared *in situ* upon treatment of rhodium precursors with silver salts.

The reaction proceeded smoothly at 110 °C in toluene to give 4-methyl-*N*-[2-(pyridin-2-yl)phenyl]benzenesulfonamide (**4aa**) in 77% yield after 12 h when *p*-toluenesulfonyl azide was used as the amido source (entry 5). While the product yield was decreased at lower temperature in toluene (entry 6), the highest product yields were obtained in 1,2-dichloroethane (DCE), even at 80 °C (entry 7), and other solvents gave

Received: April 12, 2012
Published: May 24, 2012

   dx.doi.org/10.1021/ja303527m | *J. Am. Chem. Soc.* 2012, 134, 9110−9113

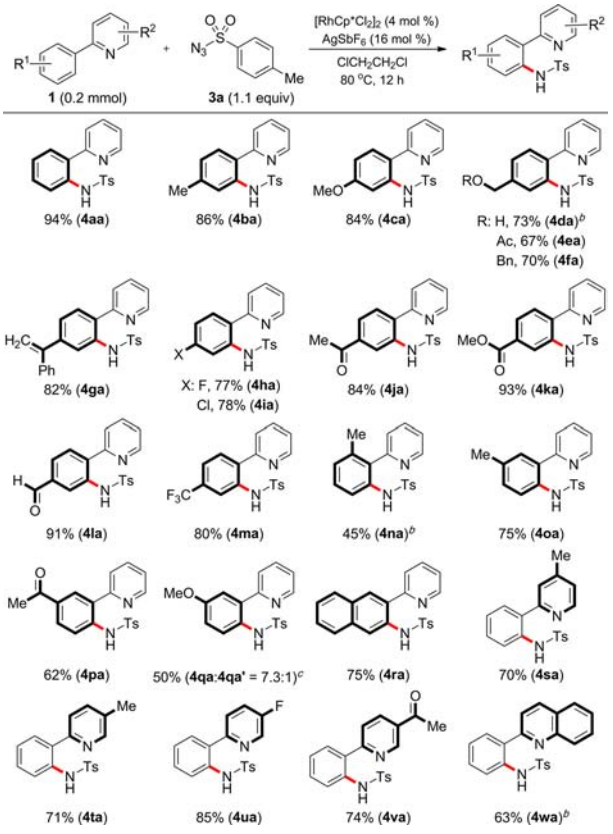
Table 1. Optimization of the Rh-Catalyzed Amidation[a]



entry	catalyst system (mol %)	solvent	temp (°C)	yield (%)[b]
1	$Rh_2(O_2CCF_3)_4$ (4)	toluene	110	11
2	$[Rh(cod)Cl]_2$ (4)	toluene	110	10
3	$[Rh(cod)Cl]_2$ (4)/$AgSbF_6$ (8)	toluene	110	20
4	$[RhCp^*Cl_2]_2$ (4)	toluene	110	10
5	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (16)	toluene	110	77
6	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (16)	toluene	80	59
7	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (16)	1,2-DCE	80	96
8	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (16)	*t*-amylOH	80	45
9	$[RhCp^*Cl_2]_2$ (4)/$AgBF_4$ (16)	1,2-DCE	80	54
10	$[RhCp^*Cl_2]_2$ (4)/KPF_6 (16)	1,2-DCE	80	<1
11	$[RhCp^*Cl_2]_2$ (2.5)/$AgSbF_6$ (10)	1,2-DCE	80	84
12	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (16)	1,2-DCE	50	27
13	$[RhCp^*(MeCN)_3][SbF_6]_2$ (8)	1,2-DCE	80	64
14	$[Ru(p\text{-cymene})Cl_2]_2$ (4)/ KPF_6 (16)	1,2-DCE	80	n.r.
15	$Pd(OAc)_2$ (8)/$PhI(OAc)_2$ (110)	1,2-DCE	80	n.r.

[a] **1a** (0.2 mmol), **3a** (1.1 equiv), catalyst, additive, and solvent (0.5 mL) at the indicated temperature for 12 h. [b] NMR yield.

Table 2. Substrate Scope of 2-Phenylpyridine Derivatives[a]



[a] In 1,2-DCE (0.5 mL) at 80 °C for 12 h (isolated yields). [b] For 48 h. [c] Structure of the major product is shown.

inferior yields (entry 8). Not surprisingly, the nature of the cationic generator was also influential. While silver hexafluoroantimonate was most effective, alteration of the cationic or anionic part of the additive gave reduced efficiency (entries 9 and 10). Although satisfactory product yield was obtained with lower catalyst loading (entry 11), reactions at lower temperature (e.g., 50 °C) became sluggish (entry 12). The fact that the use of a pregenerated cationic rhodium species afforded **4aa**, albeit in slightly lower yield (entry 13), suggests that $[Cp^*Rh(III)](SbF_6)_2$ is indeed a catalytically active species. Other transition metals such as ruthenium or palladium complexes, which are known to be highly effective in direct C−H bond functionalizations,[18] were ineffective in the present direct *N*-arylation (entries 14 and 15).

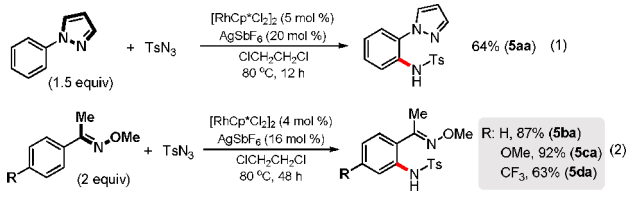
We next examined the substrate scope of various substituents to react with sulfonyl azides under the optimized conditions. Electronic variation of substituents at the arene moiety of 2-phenylpyridines had little effect on the reaction efficiency. In fact, *ortho*-amidated 2-phenylpyridine products having electron-donating substituents such as methyl (**4ba**) or methoxy (**4ca**) were obtained in good yields (Table 2).

While an unmasked hydroxyl group was compatible with the present conditions (**4da**), substrates protected with acetyl or benzyl groups underwent amidation with similar efficiency (**4ea**, **4fa**). The reaction was highly chemoselective in that olefinic double bonds, a potential reacting site, were inert (**4ga**). In addition, functional groups commonly used in organic synthesis were totally tolerated. For example, substrates bearing fluoro (**4ha**), chloro (**4ia**), ketone (**4ja**), ester (**4ka**), or aldehyde (**4la**) groups were all smoothly amidated in high yields. The amidation was highly selective, occurring exclusively at the *ortho*-position relative to the 2-pyridyl, even in the presence of other potential chelate groups such as ketone or ester (**4ja**−**4la**).[16e]

Substrates bearing electron-withdrawing groups such as trifluoromethyl (**4ma**) underwent the amidation in high yield. On the other hand, an *ortho*-substituent at the phenyl moiety slightly decreased the reactivity, presumably due to steric reasons (**4na**). Although amidation of substrates substituted at the *meta*-position with methyl (**4oa**) or acetyl (**4pa**) occurred selectively at the sterically more accessible C−H bonds, a substrate having a MeO group underwent the reaction to afford two separable regioisomeric products in high ratio (**4qa**, **4qa′**). As anticipated, 2-(2-naphthalenyl)pyridine was amidated at the sterically less hindered position in good yield (**4ra**).

Substrates substituted on the pyridine side were also readily employed in the amidation process. The desired products were obtained in good yields when a methyl group was substituted at the 4- or 5-position of pyridine (**4sa**, **4ta**). The amidation occurred efficiently with 5-fluoro-2-phenylpyridine and 5-acetyl-2-phenylpyridine to deliver **4ua** and **4va**, respectively. The amidation of a substrate bearing a quinoline directing group also proceeded in good yield (**4wa**).

A different heterocycle (e.g., pyrazole) other than pyridine also worked well as an efficient directing group to facilitate the amidation, albeit with a moderate yield (eq 1). In addition,



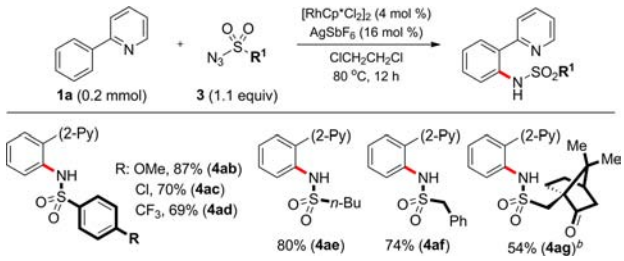
direct *N*-arylation took place at the *ortho*-position of an oxime group, which is readily accessible and easily convertible to other

dx.doi.org/10.1021/ja303527m | J. Am. Chem. Soc. 2012, 134, 9110−9113

functional groups (eq 2), thus expanding the scope of the present amidation method.

The scope of sulfonyl azides was then examined in the amidation of 2-phenylpyridine. Arenesulfonyl azide substrates substituted with methoxy (**4ab**), chloro (**4ac**), or trifluoromethyl (**4ad**) groups were readily amidated at the *ortho*-position. Aliphatic variants worked equally well, and *n*-butane-, phenylmethane-, and camphorsulfonyl azides reacted smoothly (**4ae**, **4af**, and **4ag**, Table 3).

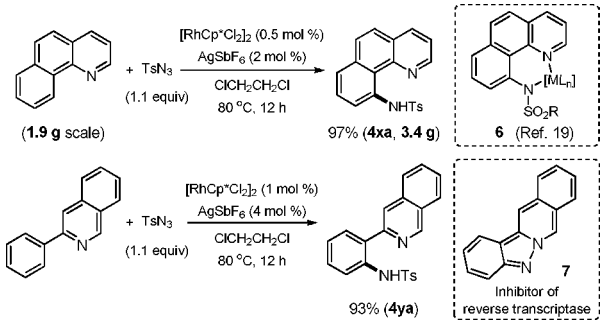
Table 3. Substrate Scope of Sulfonyl Azides[a]



[a]Isolated yields. [b]Carried out for 48 h.

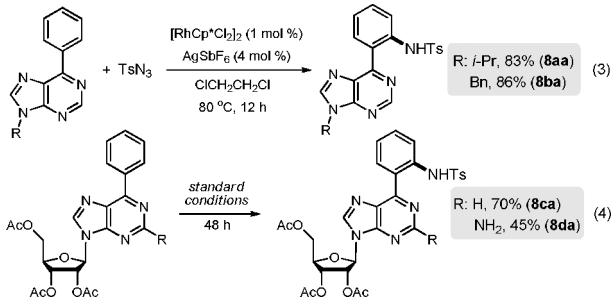
The amidated products can be useful in various areas, including organic synthesis, coordination chemistry, and the pharmaceutical industry (Scheme 2). Benzo[*h*]quinoline readily underwent direct C−H amidation using as low as 0.5 mol % of the Rh catalyst precursor. The reaction was scaled-up without difficulty, and the product **4xa** was isolated by a simple purification process (recrystallization) with N_2 as the single byproduct. Product **4xa** has utility in coordination chemistry as an effective bidentate ligand (**6**), as exemplified by Ritter's group in fluorination chemistry.[19] Selective amidation took place with 3-phenylisoquinoline using 1 mol % of the Rh species to give **4ya** in high yield, which was then used as an intermediate in the synthesis of a bioactive compound, **7**.[20]

Scheme 2. Potential Utilities of Amidated Products



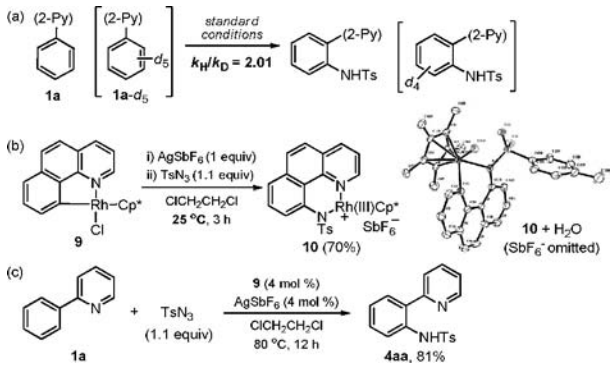
Amidation of 9-alkyl-6-arylpurines proceeded smoothly and with excellent selectivity to afford the corresponding products (**8aa**, **8ba**) in high yields using 1 mol % of the catalyst precursor (eq 3). A 6-arylpurinyl nucleoside was amidated efficiently (**8ca**, eq 4), but even a substrate bearing an unprotected aniline group underwent the amidation in an acceptable yield (**8da**). 6-Arylpurine derivatives are known to exhibit high antimycobacterial, cytostatic, and anti-HCV activities.[21]

To obtain further insights into the present direct C−H amidation, preliminary mechanistic experiments were carried out. A notable primary kinetic isotope effect (KIE, k_H/k_D = 2.01) was observed for two separate competition reactions with



1a and **1a**-d_5 (Scheme 3a), suggesting that the C−H bond cleavage is likely involved in the rate-limiting step.[22] A stable cyclometalated Rh(III) complex **9** was obtained upon treatment of benzo[*h*]quinoline with $[RhCp^*Cl_2]_2$,[23] and amido insertion into its cationic species occurred smoothly upon reacting it with TsN_3 within 3 h at room temperature (Scheme 3b). A sulfonamido rhodium **10** was isolated from this reaction and its structure unambiguously characterized by X-ray crystallographic analysis. Importantly, **9** catalyzed an amidation reaction of 2-phenylpyridine to give **4aa** in high yield (Scheme 3c), suggesting the plausible intermediacy of a cyclometalated complex in the catalytic cycle.

Scheme 3. Preliminary Mechanistic Studies

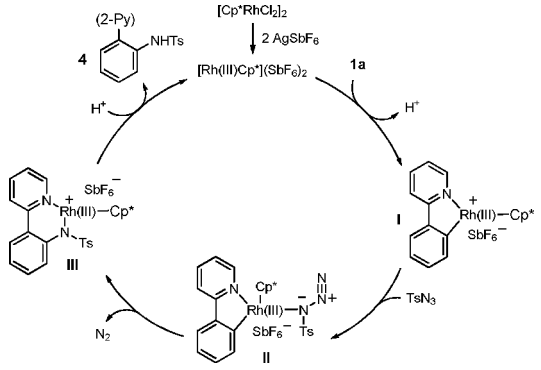


Based on the above observed data, a mechanistic pathway using 2-phenylpyridine (**1a**) and TsN_3 is proposed in Scheme 4. First, treatment of the $[RhCp^*Cl_2]_2$ precursor with $AgSbF_6$ additive generates a cationic Rh(III) species, which facilitates the key C−H bond activation to afford a five-membered rhodacyclic intermediate **I**, an structural analogue of isolated **9** (Scheme 3b). Coordination of azide to **I** leading to **II** is assumed to follow before the subsequent insertion of a sulfonamido moiety into the rhodacycle.[24] This amido transfer will provide Rh(III) amido complex **III**, an analogue of the fully characterized complex **10** (Scheme 3b). Finally, protonolysis of **III** delivers the desired product **4**.

In summary, we have developed a rhodium-catalyzed direct amidation of arenes using sulfonyl azides as the amine source, which is proposed to proceed via chelation-assisted C−H bond activation. A range of arene substrates were selectively amidated in high yields with excellent functional group tolerance. The amidation requires no external oxidants and releases N_2 as the single byproduct, thus offering an environmentally benign C−N arylation procedure that can be readily scaled-up. The synthetic utility of amidated products is enormous in such areas as organic synthesis, coordination chemistry, materials science, and medicine.

dx.doi.org/10.1021/ja303527m | *J. Am. Chem. Soc.* 2012, 134, 9110−9113

Scheme 4. Proposed Reaction Pathway



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures; data for new compounds, including ^{1}H, ^{13}C NMR, and X-ray analysis. 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.

■ ACKNOWLEDGMENTS

Korea Research Foundation (KRF-2008-C00024, Star Faculty Program) and MIRC (NRF-2012-0000912) are appreciated.

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