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Rhodium(III)-Catalyzed C−H Activation and Amidation of Arenes Using *N*-Arenesulfonated Imides as Amidating Reagents

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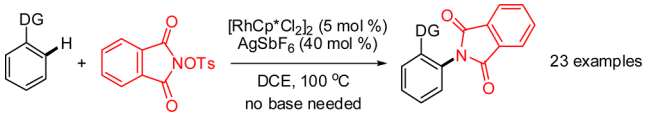
ABSTRACT



Rhodium(III)-catalyzed C−H activation−amidation of arenes bearing chelating groups has been achieved using *N*-arenesulfonated imides as efficient amidating reagents without using any base additive. Pyridine, oxime, and pyrimidine proved to be viable directing groups.

C−N bonds are a key linkage in organics, pharmaceuticals, and materials. Various methods for catalytic C−N couplings such as the Buchwald−Hartwig coupling, the Ullman coupling, and the Chan−Lam coupling have been developed.[1] These systems utilize aryl halides/tosylates or boronic acids as a coupling partner. With increasing interest in catalytic activation of C−H bonds,[2] it is important to take advantage of the ubiquity of C−H bonds for C−N coupling. Hence considerable studies on the amination of C−H bonds have been performed using Pd[3] and Cu[4] catalysts under oxidative conditions.

Alternatively, there have been increasing studies using internal oxidizing N−O and N−halogen groups for overall redox-neutral amination reactions.[5] Despite the progress, because of the structural diversity and specificity of arene substrates, it is necessary to develop amination reactions catalyzed by other transitional metals. In this context, Rh(III) complexes have been successfully employed as

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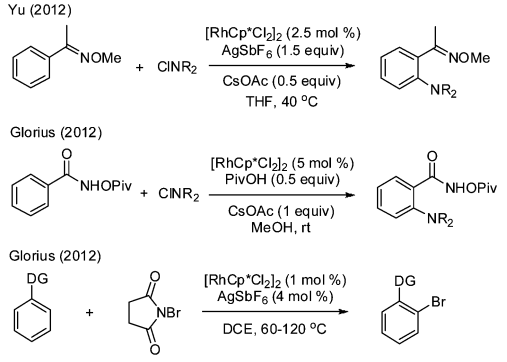
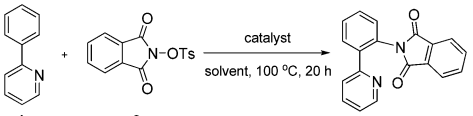
highly efficient and selective catalysts to entail amination via a C−H activation pathway[6] using isocyanates,[7] amine chlorides (Scheme 1),[8] sulfonylazides,[9] and NFSI.[10] While oxidizing N−O groups consistently effected C−H amination,[11] both amination and halogenation of C−H bonds have been achieved for N−halogen groups. For example, NFSI is known as both an amidating and a fluorinating reagent.[12] In 2012, Glorius et al. reported the highly efficient Rh(III)-catalyzed bromination of a broad spectrum of arenes using NBS (Scheme 1).[13] We reasoned that electrophilic *N*-OTs imides should be suitable amidating reagents because, in comparison to the N−Br bond in NBS, the N−O bond is more polarized or even inversely polarized by a more electronegative OTs group. Therefore, replacing the Br group in NBS with an OTs group should switch the selectivity from C−H bromination to amidation.

Scheme 1. Rh(III)-Catalyzed Coupling of C−H Bonds with N−Halogen Groups



We initiated our studies with the screening of the conditions for the coupling of 2-phenylpyridine and *N*-OTs phthalimide, a readily available source of N−O bond (Table 1). While no coupling occurred when $[RhCp^*Cl_2]_2$ (5 mol %) alone was used as a catalyst (DCE, 100 °C), addition of $AgSbF_6$ (20 mol %) can effect a smooth C−N coupling, and product **3aa** was isolated in 69% yield (entry 2). Product **3aa** was fully characterized, including by X-ray crystallography. Screening of the solvent gave DCE as an optimal one, while lower isolated yields were obtained when this reaction was performed in other solvents including DCM, PhCl, 1,4-dioxane, and acetic acid (entries 2−6). The amount of $AgSbF_6$ played an important role. Thus an optimal isolated yield of 83% was obtained when the amount of $AgSbF_6$ was doubled (entry 7). Lowering the catalyst loading to 3 mol % resulted in a reduced yield of **3aa** (entry 8), and a comparably unfavorable yield was obtained when the reaction temperature was lowered to 80 °C (entry 9). In contrast to the smooth coupling of this *N*-OTs phthalimide, essentially no reaction occurred for *N*-OAc and *N*-OC(O)Ph phthalimides, likely due to reduced electrophilicity. Given that a Ru(II) complex can be an alternative catalyst for C−N coupling reactions,[14] $[Ru(p\text{-cymene})Cl_2]_2$ was used under otherwise the same conditions. Unfortunately, although the selectivity of this reaction remains high, product **3aa** was isolated in only 63% yield due to lower conversion (entry 10), indicating the superiority of Rh(III) catalysis in this system.

Table 1. Optimization Studies[a]



1a 2a 3aa

entry	catalyst (mol %)	$AgSbF_6$ (mol %)	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$ (5)	0	DCE	0
2	$[Cp^*RhCl_2]_2$ (5)	20	DCE	69
3	$[Cp^*RhCl_2]_2$ (5)	20	DCM	61
4	$[Cp^*RhCl_2]_2$ (5)	20	AcOH	<5
5	$[Cp^*RhCl_2]_2$ (5)	20	PhCl	65
6	$[Cp^*RhCl_2]_2$ (5)	20	dioxane	53
7	$[Cp^*RhCl_2]_2$ (5)	40	DCE	83
8	$[Cp^*RhCl_2]_2$ (3)	40	DCE	72
9	$[Cp^*RhCl_2]_2$ (5)	40	DCE	70[c]
10	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	40	DCE	63

[a] Reaction conditions: 2-phenylpyridine (0.2 mmol), *N*-OTs phthalimide (0.3 mmol), solvent (2 mL), catalyst, $AgSbF_6$ additive, 100 °C, 20 h, sealed tube under Ar. [b] Yields refer to isolation after chromatography. [c] 80 °C.

With the optimized conditions in hand, we set out to explore the scope and generality of this coupling system. When a simple pyridine ring was used as a directing group for the coupling with **2a**, introduction of various

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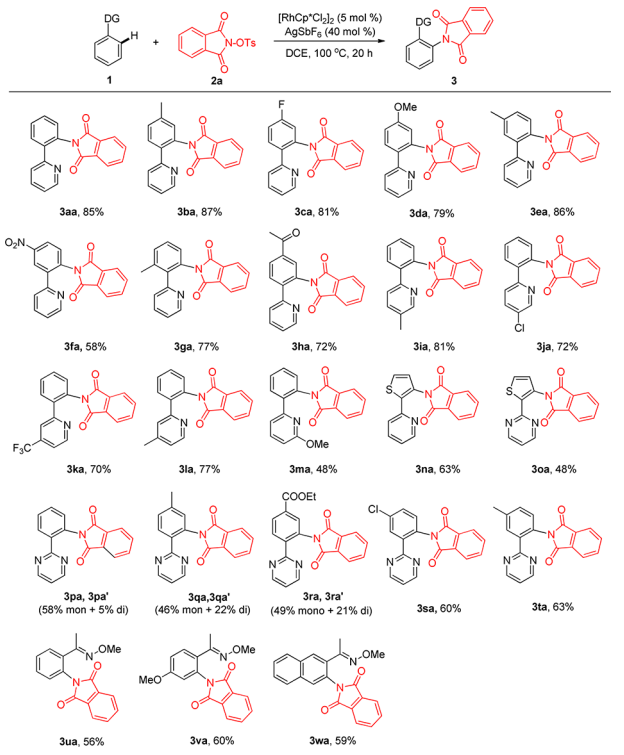
Scheme 2. Scope of Arene Substrates in Amidation Using *N*-OTs Phthalimide[a,b]

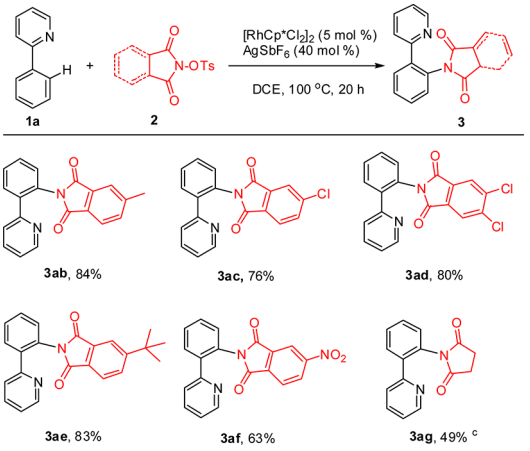


[a] Reactions conditions: arene (0.2 mmol), *N*-OTs phthalimide (0.3 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (40 mol %), DCE (2 mL), 100 °C, 20 h, sealed tube under argon. [b] Isolated yield after chromatography.

electron-donating (**3ba**, **3da**, **3ea**, **3ga**), -withdrawing (**3fa**, **3ha**), and halogen (**3ca**) groups into different positions of the phenyl ring is well tolerated, and the amidation product was isolated in 58−87% yield (Scheme 2). In particular, the isolation of product **3ga** in good yield indicated the steric tolerance of this system. The presence of a nitro group in the coupled product **3fa** can allow further functionalization. Besides using the simple pyridine directing group, the reaction tolerated pyridine rings functionalized with a variety of electron-donating (**3ia**, **3la**, **3ma**), -withdrawing (**3ka**), and halogen (**3ja**) groups at different positions, and the C−N coupled products were isolated in 48−81% yield. In all such cases, only monoamidation was observed. In contrast, introduction of a pyrimidine directing group resulted in competitive mono- and diamidation as a result of facile coordination and cyclometalation, although the monoamidation product remained the major one isolated in moderate yield. Exclusive monoamidation was achieved when a meta blocking group was introduced (**3sa**, **3ta**). We next explored the replacement of these heterocyclic directing groups with more readily available and more synthetically useful directing groups. Thus the *O*-Me oxime proved to be a viable directing group, and the amidation product was isolated in moderate to good yield (**3ua**−**3wa**). Besides C−H activation in benzene rings, the C−H activation can be smoothly extended to heterocyclic systems. Thus the same coupling reaction was applicable to pyridyl- and pyrimidyl-functionalized thiophene, albeit with a relatively lower conversion (**3na**, **3oa**), and no amidation in the pyridine ring was detected.

To demonstrate the scope of the imide substrate, different *N*-OTs imides were applied as coupling partners in the reaction with 2-phenylpyridine. Thus *N*-OTs phthalimides with different electron-donating and -withdrawing substituents in the backbone reacted smoothly with comparably high efficiency (**3ab**−**3af**, Scheme 3). In contrast, *N*-OTs succinimide gave poor reactivity, which is likely ascribable to the lower electrophilicity with this saturated imide backbone. Indeed, switching to the more electrophilic *N*-OTf succinimide afforded a moderate yield of the amidation product **3ag**.

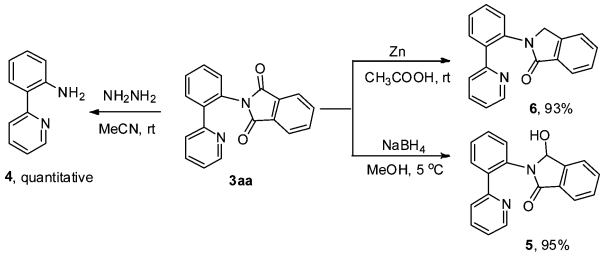
Scheme 3. Scope of *N*-Arenesulfonated Imides in C−H Amidation[a,b]



[a] Reactions conditions: 2-phenylpyridine (0.2 mmol), imide (0.3 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (40 mol %), DCE (2 mL), 100 ·C, 20 h, sealed tube under argon. [b] Isolated yield after chromatography. [c] *N*-OTf succinimide was used.

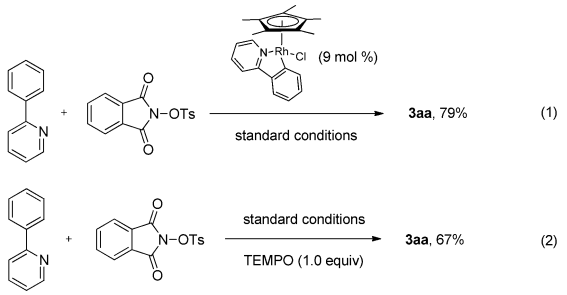
To demonstrate the synthetic usefulness of this coupling reaction, facile and high-yielding derivatization of product **3aa** has been performed (Scheme 4). Treatment of **3aa** with hydrazine led to the quantitative formation of primary amine **4**. Partial reduction using $NaBH_4$ readily gave an alcohol **5**, while Zn/AcOH treatment afforded a further reduced product **6**.

Scheme 4. Derivatization of a Coupled Product



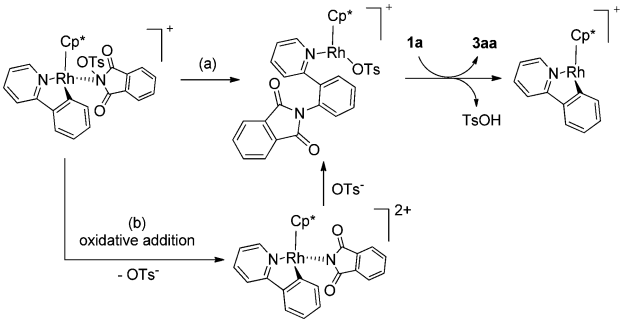
Several experiments have been performed to probe the reaction mechanism. To explore the relevance of

cyclometalation, a cyclometalated RhCp*(N̂C)Cl complex was prepared and was applied as a catalyst precursor (9 mol %), which catalyzed this reaction with a comparable efficiency under the same catalytic conditions (eq 1). This suggests the relevancy of C−H activation. The kinetic isotope effect was next studied in an intermolecular competitive coupling of **2a** with an equimolar mixture of **1a** and **1a**-d_5. ^{1}H NMR analysis of the isolated product gave KIE = 1.1 (see the SI). This small value suggests that the C−H bond cleavage is not likely involved in the rate-limiting step, which is in contrast to those reported in other Rh(III)-catalyzed amination reactions.[8,11] Since the N−O bond in the imide might undergo hemolytic cleavage, we next probed the possibility of radical species in this reaction. Addition of TEMPO (1.0 equiv) to the coupling reaction of **1a** and **2a** only caused a slight decrease of the isolated yield (eq 2), indicating that a radical species is likely irrelevant.



Despite these mechanistic data, it remains a question whether this coupling proceeded via an all-Rh(III) pathway or an alternative Rh(III)−Rh(V) pathway (Scheme 5). In an all-Rh(III) pathway, after the cyclometalation was achieved, *N*-coordination of the imide is followed by nucleophilic displacement of the OTs by the Rh−C(aryl) bond (electrophilic amidation) with concerted ligation of the OTs group.[15] Alternatively, the *N*-bound imide might undergo oxidative addition to give a Rh(V) intermediate, followed by reductive elimination. A related scenario of N−O bond cleavage has been studied in Pd-catalyzed Narasaka−Heck coupling reactions.[16] Of note, although Rh(V)−Rh(III) pathways have been postulated as a possibility in some systems, no experimental evidence has been provided.[11,13,17] While no conclusion could be drawn at this stage, it should be safe to rationalize that, with two highly withdrawing groups attached to the nitrogen group, the current imide substrate is much less coordinating than those recently examined including chloroamines and aroyloxycarbamates.[8,11] Hence the lower coordinating ability and high electrophilicity of the imide substrate should argue for a higher tendency for the oxidative addition (Rh(III)−Rh(V)) pathway. Further mechanistic studies are underway.

Scheme 5. Two Possible Reaction Pathways Following Cyclometalation



In summary, we have achieved a novel Rh(III)-catalyzed C−H amidation of arenes using readily available *N*-arenesulfonated imides as amidating reagents. This reaction proceeded in the absence of any base additive. Arenes bearing pyridine, oxime, and pyrimidine directing groups are all viable substrates, and a broad spectrum of coupling partners have been established. The C−N coupled product can be further functionalized. This method may find applications in the synthesis of related arylamine compounds.

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Supporting Information Available. Detailed experimental procedures, spectroscopic data of all new products, and crystal data of **3aa** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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