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Rh[III]-Catalyzed C−H Amidation Using Aroyloxycarbamates To Give *N*-Boc Protected Arylamines

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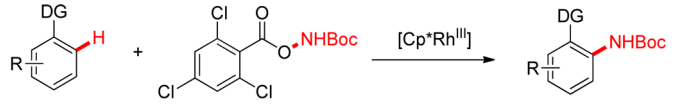
ABSTRACT



The Rh(III)-catalyzed amidation of C(sp^2)−H bonds by the use of electron-deficient aroyloxycarbamates as efficient electrophilic amidation partners is reported. The reaction proceeded under mild conditions with broad functional group tolerance, and pyridine and *O*-methyl hydroxamic acids serve as efficient directing groups, giving access to valuable *N*-Boc protected arylamines (also Fmoc and Cbz). Preliminary mechanistic experiments are discussed.

The relevance of the arylamine/aniline motif in chemistry is reflected by its ubiquity in natural products, pharmaceuticals, and countless other compounds.[1] To date, the most powerful methods for the construction of the core C_{aryl}−N bonds are represented by Ullmann and Buchwald−Hartwig couplings, using Cu or Pd catalytic systems and preactivated aryl halides.[2] With the advent and continuous advancement of transition-metal catalyzed C−H activation methods in recent years,[3] considerable research interest toward the development of metal catalyzed direct C−H amination processes has been effected.[4] Despite the continuous search for new catalytic systems, the intermolecular transformation of a C_{aryl}−H bond into the valuable arylamine C−N bond still remains challenging, being reported for activated aromatics[5a−f] and few directing group-assisted arenes under oxidative conditions.[5g−k]

As an attractive alternative, the effective use of electrophilic nitrogen sources (chloroamines, hydroxylamines, azides) containing a weak N−X bond as a coupling partner with (hetero)arenes has been demonstrated in efficient Pd[6a−c] and Cu[6d,e] catalyzed intermolecular C(sp^2)−H amination and amidation reactions under redox-neutral

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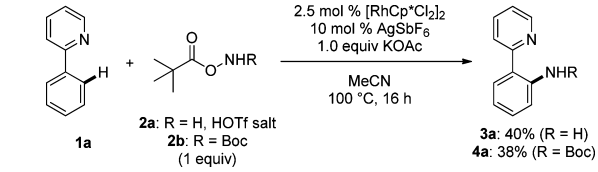
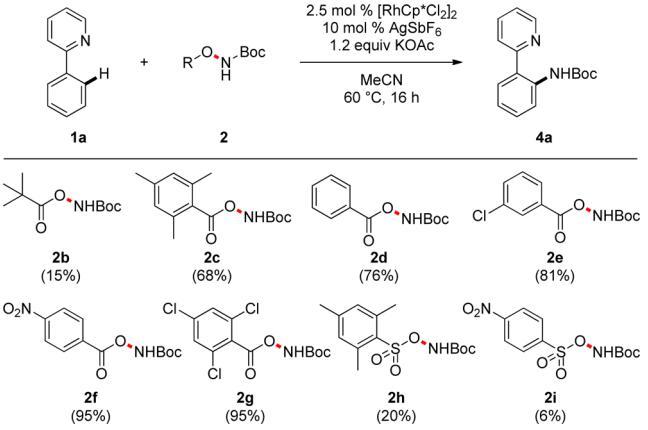
conditions. Recently, directed Rh-catalyzed methods employing chloroamines,[6f,g] aryl azides[6h] and arylsulfonyl azides,[6i,j] and NFSI[6k] have been reported to give access to arylamines and arylsulfamides. Herein, we wish to report on a mild Rh(III)-catalyzed directed *ortho*-amidation with aroyloxycarbamates giving access to *N*-Boc protected arylamines using pyridine or *O*-methyl hydroxamic acid as directing groups (DGs). In our continued interest to develop broadly applicable, mild, and efficient C−H activation methods using the Cp*Rh(III) catalyst,[7,8] we initially investigated the formation of primary aromatic amine derivatives via Rh-catalyzed C−H activation followed by electrophilic amination, inspired by a recent report on the amination of boronic acids with *O*-(2,4-dinitrophenyl)hydroxylamine.[9] While this reagent was not suitable, we found that the reaction of 2-phenylpyridine (**1a**) with 2.5 mol % $[RhCp^*Cl_2]_2$, 10 mol % $AgSbF_6$, 1.0 equiv of KOAc, and 1.0 equiv of $PivONH_2 \cdot HOTf$[10] (**2a**), in MeCN at 100 °C, produced the corresponding free aniline **3** in 40% yield (Scheme 1).

Scheme 1. Initial *o*-C−H Amination of 2-Phenylpyridine



Scheme 2. Survey of the Different Electrophilic Amidation Partners[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), KOAc (0.12 mmol), MeCN, 60 °C, 16 h. The corresponding yields of **4a** were determined by crude ^1H NMR analysis using CH_2Br_2 (7.0 μL) as an internal standard and are given in parentheses.

Furthermore, the analogous reaction with *tert*-butyl pivaloyloxycarbamate (**2b**) afforded the *N*-Boc protected derivative **4**, which can be readily deprotected to give the primary amine **3**.[11] This promising finding led us to investigate the nature of the leaving group in the amination agent in order to increase its efficiency in the desired C_{aryl}−N bond formation. A survey of electronically different *tert*-butyl aroyloxycarbamates and *tert*-butyl arylsulfonyloxycarbamates[12] **2** revealed the electron-deficient 4-nitrobenzoyl (**2f**) and 2,4,6-trichlorobenzoyl (**2g**) groups as effective substituents on the N-atom, giving the amidation product in excellent yield under relatively mild reaction conditions (Scheme 2). The sulfonyl derivatives (**2h, 2i**) showed only low conversion, although nosyloxycarbamates have been reported to be effective in a related Pd-catalyzed C−H amidation of anilides.[6a] The potential of this mild

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(11) Deprotection of **4** using TFA in CH_2Cl_2 for 3 h at rt afforded **3** in 95% isolated yield (see Supporting Information, SI).

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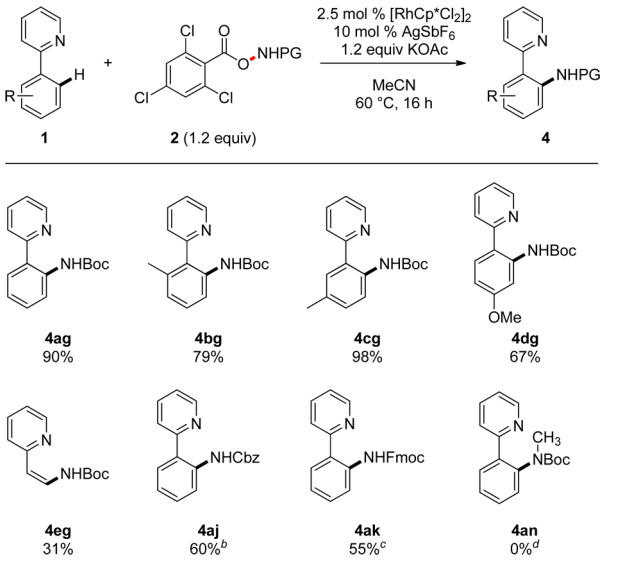
Rh(III)-catalyzed C−H amidation using *tert*-butyl(2,4,6-trichlorobenzoyl)oxycarbamate **2g** as an efficient electrophilic amidation partner was investigated next.[13,14]

As a start, different phenylpyridine derivatives were submitted to the established reaction conditions (Scheme 3). Both *ortho*- (**4bg**) and *meta*-methyl (**4cg**) substituents reacted smoothly, giving the products in high yields and as a single regioisomer in the case of **4cg**. The electron-donating *para*-methoxy group was tolerated well (**4dg**); however, a nitrile group in this position showed only negligible conversion. Encouragingly, the olefinic C−H of 2-vinylpyridine could also be amidated by this protocol, albeit in low yield (**4eg**). In addition to the *N*-Boc group, other prominent *N*-protecting groups such as the Cbz (**4aj**) and Fmoc (**4ak**) group, being removable under orthogonal conditions,[15] could also be installed via this Rh(III)-catalyzed C−H amidation. Of interest, a methyl substituent on the nitrogen of the coupling partner shuts down the reactivity, providing none of the respective secondary arylamide.

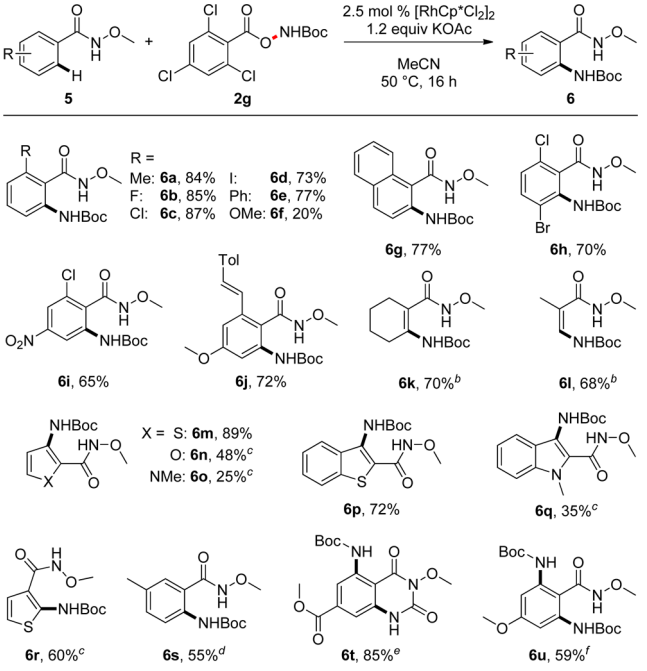
Next, we were interested in the replacement of the pyridine directing group by a more common and synthetically useful moiety. *N*-Methoxybenzamides have been shown to be powerful in combination with the Cp*Rh(III)-catalyst.[8b,i,16] To our delight, a broad scope of substrates bearing various functional groups proved to be suitable (Scheme 4). Slightly modified reaction conditions (2.5 mol % $[RhCp^*Cl_2]_2$, 1.2 equiv of KOAc and aroyloxycarbamate **2g**, MeCN, 50 °C) were used. *ortho*-Substituents like methyl, phenyl, and halides (including iodide) afforded high yields of the *N*-Boc protected arylamines (**6a**−**e**). The methoxy substituent (**6f**) in this position proved to be troublesome, possibly by competing inhibitory chelation of the Rh-catalyst. The α-naphthyl derivative also gave the corresponding product in 77% yield (**6g**). A 2,5-dihalide substituted *N*-methoxybenzamide (**6h**), as well as substrates bearing a nitro (**6i**) or styryl (**6j**) moiety, also smoothly underwent the amidation. Again, we were pleased to find that *O*-methyl hydroxamic acids bearing olefinic C−H bonds undergo the directed amidation: **6k** and **6l** were obtained in good yields even from the reaction at rt. Among heterocyclic substrates, thiophene (**6m**) and benzothiophene (**6p**) bearing the DG in the 2-position reacted with high conversion, whereas the corresponding 3-position proved less efficient (**6r**). In the cases of substrates derived from the more challenging heterocycles furan (**6n**), pyrrol (**6o**), and indole (**6q**), a higher catalyst loading and increased temperature of 60 °C were applied to obtain the amidated products in acceptable to moderate yields. For *meta*- and *para*-substituted benzhydroxamic

Scheme 3. Scope of 2-Phenylpyridine Derivatives[a]



[a] PG = Protecting group. Reaction conditions: **1** (0.25 mmol), **2g** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), KOAc (0.3 mmol), MeCN (2.5 mL), 60 °C, 16 h. Isolated yields are given. [b] With **2j** (1.2 equiv), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), 80 °C. [c] With **2k** (1.5 equiv), KOAc (1.0 equiv), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), 100 °C. [d] With **2n** (1.2 equiv).

Scheme 4. Scope of the *O*-Methylhydroxamic Acids[a]



[a] Isolated yields. Reaction conditions: **5** (0.25 mmol), **2g** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), KOAc (0.3 mmol), MeCN (2.5 mL), 50 °C, 16 h. [b] Run at rt. [c] With $[RhCp^*Cl_2]_2$ (5 mol %), 60 °C. [d] Run in MeOH (2.5 mL), 40 °C. [e] **2g** (2.5 equiv, 0.625 mmol), KOAc (4.0 equiv, 1.0 mmol), 80 °C, 16 h. [f] **2g** (2.5 equiv, 0.625 mmol), KOAc (2.5 equiv, 0.625 mmol), 40 °C, 16 h.

(13) The coupling partner **2g** was chosen over **2f** due to possible complications arising from competing coordination to the nitro group and available *o*-C−H bonds in **2f**.

(14) In analogy to **2a**, the corresponding triflate salts of *O*-mesitoylhydroxylamine (**2l**) and *O*-(2,4,6-trichlorobenzoyl)hydroxylamine (**2m**) (see SI) were prepared from **2c** and **2g**, respectively, to improve the yield of the free aniline **3**. However, no improvement (**2l**, 35% yield of **3**) or very poor conversion (**2m**, 5%) were observed.

(15) Greene, T. W.; Wuts, P. W. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

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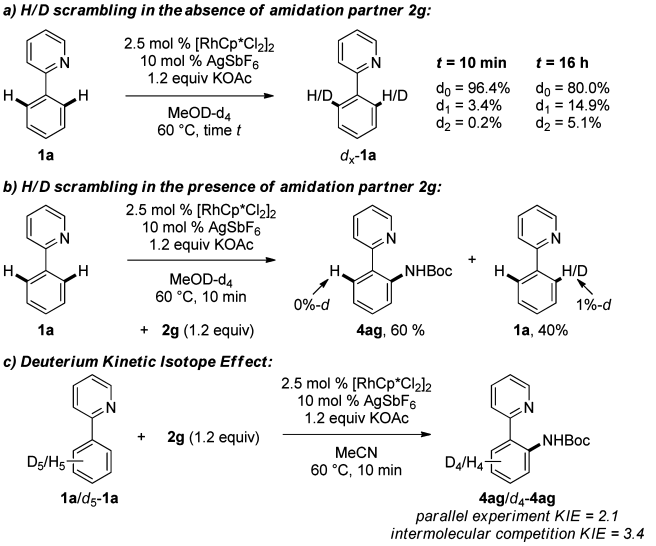
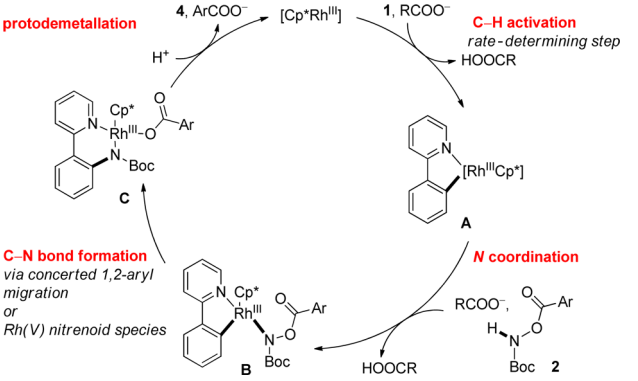
Scheme 5. Deuterium Labeling Experiments and DKIE Study



acids, diamidation was observed, leading to product mixtures.[17] For the *meta*-methyl substituted substrate **5s**, evaluation of the reaction parameters led to a maximum isolated yield of 55% of the monoamidated product **6s**. Furthermore, using 2.5 equiv of **2g**, the observed diamidation can be utilized to generate 2,6-diaminobenzamide derivatives, as demonstrated for **6u**. Upon additional heating and an excess amount of base, a cyclization is promoted, providing the interesting 3-methoxy-1*H*-quinazoline-2,4-dione structure,[18] in the case of **6t** in 85% yield. The synthetic exploitation of this finding might be of interest for future studies.

To shed light on the mechanism, deuterium labeling experiments were conducted with 2-phenylpyridine (Scheme 5). H/D scrambling in MeOD-d_4 revealed a reversible C−H rhodation in the absence of **2g**, albeit this process is slow (Scheme 5a). However, in the presence of **2g**, there is no D-incorporation observed in **4ag** (at a conversion of 60%) and only a negligible amount of d_1-**1a** formed (Scheme 5b), indicating the amidation process to be much faster than the deuteration. Furthermore, a deuterium kinetic isotope

Scheme 6. Mechanistic Considerations



effect (DKIE) of 2.1 was observed in a parallel experiment and a DKIE of 3.4 in an intermolecular competition experiment[19] of **1a**/d_5-**1a** (Scheme 5, c), suggesting C−H bond activation to be the rate-determining step.

A preliminary mechanistic pathway is postulated (Scheme 6): Coordination of the nitrogen directing group (pyridine-N or hydroxamate-N) to the rhodium catalyst precedes the C−H activation step, which gives rhodacycle **A** upon proton abstraction. Next, the aroyloxycarbamate **2** coordinates to the rhodacycle via its deprotonated nitrogen to afford rhodacycle **B**. The next step delivers the C−N bond: a concerted mechanism involving a 1,2-aryl migration on the amide nitrogen with concomitant N−O cleavage is conceivable. Alternatively, a stepwise reaction via a Rh(V) nitrenoid species (obtained by *O*-acylmigration) followed by reductive elimination to give complex **C** is possible.[20] The product **4** is deliberated by protodemetalation, restoring the Rh(III)-catalyst.

In conclusion, a novel Rh(III)-catalyzed C(sp^2)−H amidation using electron-deficient aroyloxycarbamates as an efficient electrophilic nitrogen source to give access to *N*-carbamate protected arylamines under mild reaction conditions has been described. We expect this method to find applications in the synthesis of biologically active arylamine compounds.

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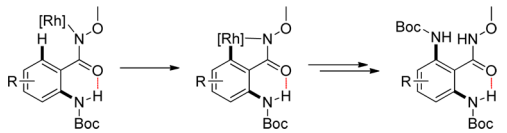
Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) A possible hydrogen bonding between the carbonyl oxygen of the DG and the amide N−H in the first-formed monoamidated product might account for the observed diamidation reactivity when two *o*-C−H bonds are available:



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