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Mechanistic Studies of the Rhodium-Catalyzed Direct C−H Amination Reaction Using Azides as the Nitrogen Source

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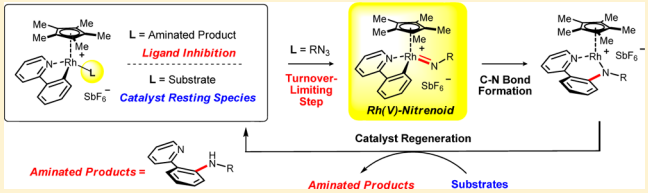
Supporting Information

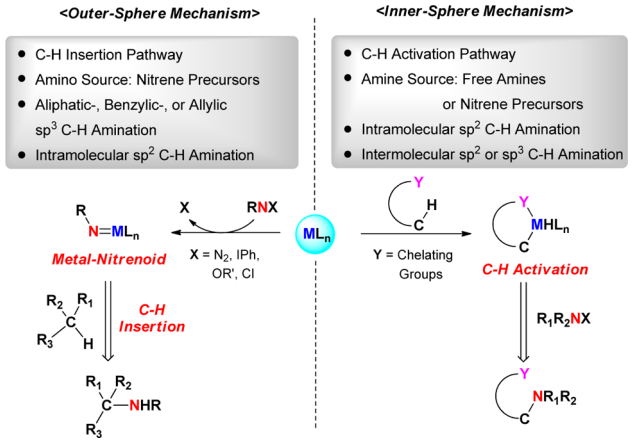
ABSTRACT: Direct C−H amination of arenes offers a straightforward route to aniline compounds without necessitating aryl (pseudo)halides as the starting materials. The recent development in this area, in particular in the metal-mediated transformations, is significant with regard to substrate scope and reaction conditions. Described herein are the mechanistic details on the Rh-catalyzed direct C−H amination reaction using organic azides as the amino source. The most important two stages were investigated especially in detail: (i) the formation of metal nitrenoid species and its subsequent insertion into a rhodacycle intermediate, and (ii) the regeneration of catalyst with concomitant release of products. It was revealed that a stepwise pathway involving a key Rh(V)−nitrenoid species that subsequently undergoes amido insertion is favored over a concerted C−N bond formation pathway. DFT calculations and kinetic studies suggest that the rate-limiting step in the current C−H amination reaction is more closely related to the formation of Rh−nitrenoid intermediate rather than the presupposed C−H activation process. The present study provides mechanistic details of the direct C−H amination reaction, which bears both aspects of the inner- and outer-sphere paths within a catalytic cycle.



INTRODUCTION

Nitrogen-containing compounds are widely present in natural products and synthetic intermediates.[1] In particular, N-aryl compounds (anilines) are a key building unit in medicinal and materials chemistry.[2] As a result, the development of efficient and selective C−N bond-forming reactions has been a highly important research topic in chemical synthesis. Although some metal-free conditions have been examined for the amination reactions,[3] metal-mediated procedures offer notable advantages in terms of reaction conditions, selectivity, practicability, and substrate scope. Representative procedures in this approach include the copper-mediated amination (Ullmann reaction)[4] and palladium-catalyzed N-arylation of aryl halides (Buchwald−Hartwig coupling).[5] Mainly because of the tailor-made design of suitable ligands, synthetic utility of the latter method has been significantly widened even for industrial applications.[6] Despite these notable features, however, they require aryl (pseudo)halides as the prefunctionalized starting materials to react with amines (amides). In this regard, an alternative route to N-substituted anilines has been scrutinized directly using arenes as a reactant especially in recent years. Two approaches can be conceived in the metal-catalyzed direct C−H amination of arenes (Scheme 1).[7] A path based on nitrenoid transfer from metal center to C−H bonds has been extensively investigated by using certain metal species (outer-sphere mechanism).[8] A number of nitrene precursors can be utilized in this case such as azides,[9] hypervalent iminoiodinanes (in situ generated from hypervalent iodine reagents),[10] hydroxylamines,[11] or halogenated amines.[12] Whereas this approach has been successfully applied in the amination of aliphatic, benzylic, or allylic sp^3 C−H bonds,[13] examples of arene C−H amination are limited mainly to intramolecular reactions.[14]

Scheme 1. Two Pathways in the Direct C−H Amination



The second approach in the direct C−H amination is based on the C−H bond activation path with low valent metal species (inner-sphere mechanism).[15] This reaction turned out to be

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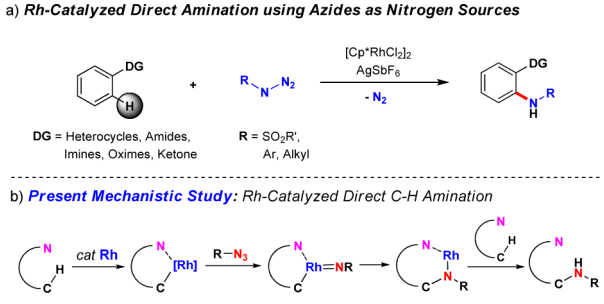
especially efficient and selective for chelation group-containing substrates presumably due to the formation of a metallacyclic intermediate. There are two reaction conditions for the subsequent C−N bond formation depending on the type of amine reactants. Whereas parent amines can be directly employed in the presence of external oxidants,[16,17] the use of preactivated amino precursors allows an oxidant-free procedure for the amination.[18−20] For this purpose, a range of amino precursors are examined such as hydroxylamines,[18] halogenated amines,[19] and azides.[20]

Recently, we have developed the rhodium-catalyzed intermolecular direct C−H amination of arenes using organic azides as the unique amino source (Scheme 2a).[20,21] The amination

Scheme 2. Rh(III)-Catalyzed C−H Amination with Azides

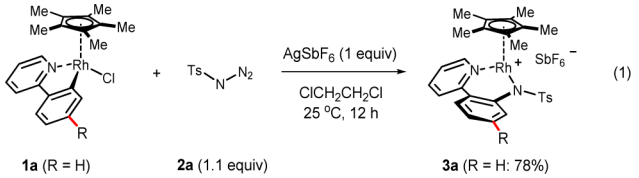


was performed best with cationic Cp*Rh(III) catalyst[22] generated in situ from $[Cp^*RhCl_2]_2$ and silver additive in nonpolar solvents at temperatures between 50 and 110 °C depending on substrates employed.

This reaction protocol does not require external oxidants and releases only molecular nitrogen as a byproduct. A wide range of directing groups were effective for this reaction furnishing desired *ortho*-aminated products in good yields with excellent selectivity, and functional group tolerance was also high under the developed conditions. In addition, the azide scope was very broad, and, therefore, sulfonamido, arylamino, and alkylamino moieties were readily installed at the desired position of arene substrates by employing the corresponding azides. Described herein are mechanistic details of the Rh-catalyzed direct intermolecular C−H amination of arenes with organic azides (Scheme 2b).[23]

RESULTS AND DISCUSSION

Reaction Intermediates. We initially investigated the feasibility of a rhodacycle species as an intermediate in a plausible amido insertion process. Stable metallacycle complexes **1a,b** were prepared according to the Jones procedure[24] in a stoichiometric reaction of $[Cp^*RhCl_2]_2$ with 2-phenylpyridine and 2-(4-methoxyphenyl)pyridine, respectively. When a mixture of **1a** (or **1b**) and *p*-toluenesulfonyl azide (**2a**) was treated with silver hexafluoroantimonate, the corresponding amido insertion complexes **3a** and **3b** were obtained in high yields at room temperature in 1,2-dichloroethane (eq 1).[25] As



(1)

we previously reported,[20] a silver salt was added to convert the neutral rhodium complexes (**1a,b**) to their cationic species, and $AgSbF_6$ was the most effective among various silver salts examined.

Although the isolated complexes **3a,b** were not highly stable at ambient atmosphere, we were able to obtain their crystallographic structure by slow diffusion of diethyl ether into an acetone solution containing the complexes (Figure 1).

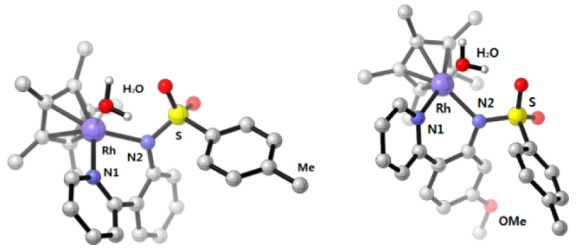
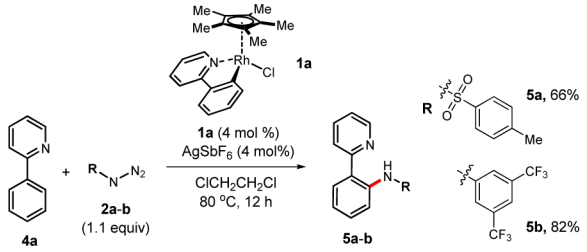


Figure 1. X-ray structure and atom labeling schemes for cationic **3a**−H_2O (left) and **3b**−H_2O (right). All hydrogen atoms and SbF_6 anion are omitted for clarity.

As expected, the crystal structure of **3a** showed a piano stool geometry with bidentate coordination of two nitrogen atoms to the metal center (selected interatomic distances (Å) in **3a**: Rh−N1 = 2.097, Rh−N2 = 2.136, Rh−O = 2.198). One molecule of water was observed to occupy the sixth coordination. In the methoxy analogue of **3b**, Rh−N1 bond length was slightly longer, while Rh−N2 and Rh−O bonds were slightly shorter than those of **3a**.

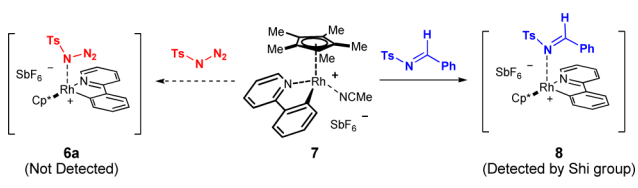
Catalytic activity of the isolated rhodacyclic complex **1a** was next examined under the previously developed amination conditions.[20a] Amination of 2-phenylpyridine (**4a**) took place smoothly with either *p*-toluenesulfonyl azide (**2a**) or 3,5-bis(trifluoromethyl)phenyl azide (**2b**) in the presence of a catalytic amount (4 mol %) of complex **1a** and $AgSbF_6$, leading to the desired products **5a** (66%) and **5b** (82%), respectively (eq 2).



(2)

Because the coordination of organic azides to various metal complexes such as palladium, iridium, silver, and copper was previously reported,[26] we also presumed that the amination occurs via the initial azide coordination to a cationic rhodium species leading to **6a** (Scheme 3). In fact, Shi et al. recently

Scheme 3. Detection of Amino Group-Bound Rhodacycle



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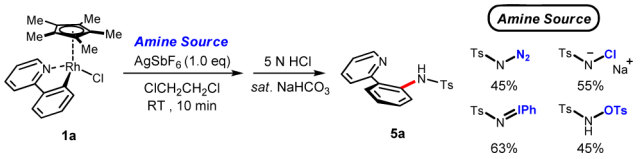
reported the observation of an imine-bound cationic rhodium species **8** from a pregenerated rhodium complex **7**.[23d,27] They investigated a ligand exchange process prior to the insertion of a rhodacyclic bond to bound sulfonylaldimine by using in situ ESI–MS and ^{1}H NMR spectroscopy. However, we could not detect an azide-coordinated species with various tools including ^{1}H NMR and mass spectroscopy. Instead, mass peaks corresponding to the unsaturated cationic rhodium species **7** were observed along with the amido insertion complexes (**3a**, see the Supporting Information for details).

C–N Bond Formation with Various Amino Precursors. The observation that the amido insertion step (eq 1) took place smoothly upon treatment of a rhodacycle **1a** with sulfonyl azide (**2a**) prompted us to scrutinize additional aspects of this conversion. Because it is known that a range of amine precursors such as iminoiodinanes, haloamines, or sulfonyloxyamines undergo a nitrenoid-forming process under suitable conditions,[10b,19b,c,28] we thus employed such amino precursors in a stoichiometric conversion of **1a** to **5a** (Scheme 4). All

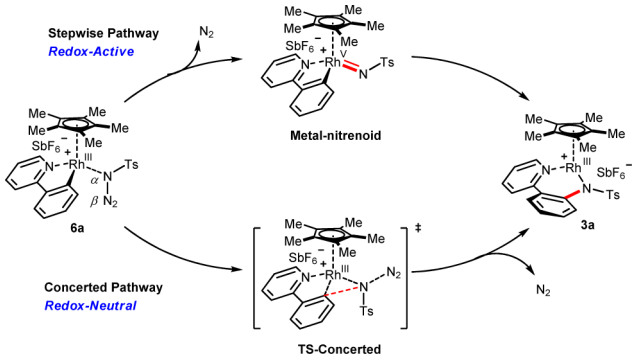
Scheme 4. Stoichiometric Amination with Various Amino Sources



precursors bearing a tosylamido moiety smoothly reacted with **1a** at room temperature upon the addition of $AgSbF_6$. Similar yields of **5a** were obtained from the reactions employing TsNIPh, TsNCl(Na), and TsNH(OTs) when compared to that with TsN_3.

We envisaged two possible pathways for this insertion process: stepwise and concerted route (Scheme 5). In a

Scheme 5. Two Plausible Pathways in the Insertion of "NR"

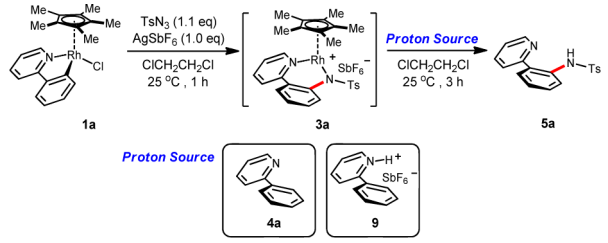


stepwise pathway, initial coordination of azide to a rhodium center (**6a**) is assumed to occur followed by release of N_2 to form a discrete metal–nitrenoid intermediate (redox-active),[29] and then a collapse of this intermediate will afford the insertion product (**3a**). In fact, the formation of a metal–nitrenoid species has been well documented in a list of metal-mediated nitrogen transfer reactions using the above amino precursors.[19b,c,28] On the other hand, an amido insertion can be coincided with the loss of nitrogen molecule without the formation of a metal–nitrenoid species. This concerted process is assumed to proceed via a transition state (**TS-Concerted**) of a three-centered interaction between the rhodium, phenyl carbon, and azide nitrogen atom.[25a,b] One of the most notable differences between these two pathways would be in the change of oxidation state of the rhodium metal center during the course of the amido insertion. Whereas the higher oxidation state of Rh(V)[30,31] is assumed to be involved in the stepwise pathway, the concerted route is redox neutral. Our efforts to detect a plausible change in the oxidation state of the metal center using various tools including an electrochemical method were not successful.

Catalyst Regeneration and Inhibitory Effects of Aminated Products. With the above mechanistic information on the C–N bond formation in hand, we investigated the late stage of the plausible catalytic cycle: a protodemetalation process to release products with the concomitant catalyst regeneration. To liberate aminated products from the amido insertion complexes (representatively **3a** and **3b** in eq 1), a proton source needs to be supplied for this process. Inspired by the previous experiments by Sanford[25a] and Shi,[23d] we examined a range of potential proton sources. Sanford et al. showed that strong acids such as trifluoroacetic acid or hydrochloric acid can be utilized to release aminated products from palladium sulfonamido species. On the other hand, in the Rh-catalyzed imine insertion to 2-phenylpyridines, Shi and coworkers elucidated that either 2-phenylpyridine or acetic acid can work as a proton source.

Because of difficulty in handling the inserted sulfonamido rhodium complexes (e.g., **3a** or **3b**), a one-pot protodemetalation experiment was designed without need to employ the isolated labile species (Table 1). When an in situ formed

Table 1. Protodemetalation with Plausible Proton Sources



entry	proton source (equiv)	**5a** (%)[a]
1	**4a** (2)	27
2	**4a** (10)	46
3	**9** (2)	4
4	**4a** (8)/**9** (2)	45

[a] ^{1}H NMR yield (internal standard: 1,3-benzodioxole).

tosylamido inserted rhodium complex **3a** was treated with 2-phenylpyridine (**4a**, 2 equiv) at room temperature, an amidated product (**5a**) was provided albeit in moderate efficiency (entry 1). The yield was increased with higher loading of **4a** (entry 2), suggesting that the substrate itself serves as a proton source. In contrast, the efficiency of this protodemetalation became poorer with pyridinium salt **9**, independently obtained from 2-phenylpyridine and $AgSbF_6$ in THF (entry 3).[23c] In addition, a combined use of **4a** and **9** did not much alter the protodemetalation process (entry 4). These results suggest that 2-phenylpyridine substrate (**4a**) works as a proton donor more efficiently than its pyridinium salt **9**. As a result, we propose that an aminated product is released by an interaction of amido inserted rhodacycle with 2-phenylpyridine substrate

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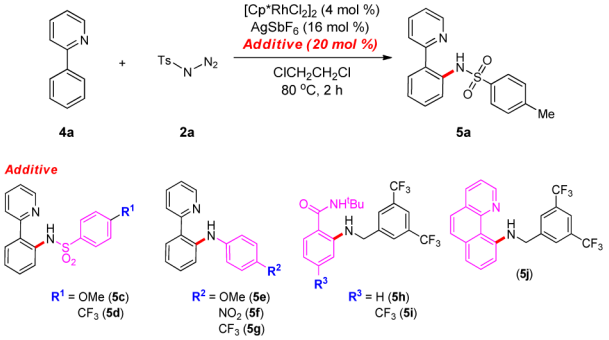
accompanied by the regeneration of an active rhodacycle species.

One of the highly interesting features of the current amination reaction is the fact that products bear an additional coordinating amino group. This aspect led us to investigate the presupposed inhibitory effects of aminated products on the reaction progress (Table 2).

Table 2. Inhibitory Effects with Various Aminated Products[a]



entry	additive	5a (%)[b]	entry	additive	5a (%)[b]
1	none	53	6	**5f**	56
2	**5a**	35	7	**5g**	49
3	**5c**	38	8	**5h**	37
4	**5d**	38	9	**5i**	50
5	**5e**	<1	10	**5j**	21

[a]Conditions: **4a** (0.1 mmol), **2a** (1.1 equiv), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), additive (20 mol %) in $ClCH_2CH_2Cl$ (0.5 mL) for 2 h at 80 °C. [b]^1H NMR yield (internal standard: 1,3-benzodioxole).

Reaction progress at an early stage was monitored in the presence of preisolated sulfonamidated compounds substituted with 4-methyl (**5a**), 4-methoxy (**5c**), and 4-trifluoromethyl (**5d**) groups (entries 2–4). A similar level of inhibitory effects was observed for those additives to suggest that the electronic property of substituents little affected the binding affinity of amidated compounds to the Rh metal center that leads to the inhibitory effects. In sharp contrast, a significantly different outcome was obtained with aminated additives derived from aryl azides. For instance, while the reaction was completely inhibited by **5e** (entry 5), the presence of **5f** or **5g** bearing electron-withdrawing substituents (NO_2 and CF_3, respectively) did not result in such notable inhibition (entries 6 and 7), indicating that these effects were sensitive to the electronic nature of substituents. The inhibitory effects were also displayed by additives derived from alkyl azides, and the extents were varied depending on the aminated substrates. For example, while an aminated benzamide **5h** displayed measurable inhibitory effects (entry 8), a derivative **5i** bearing a CF_3 substituent retarded the reaction only slightly (entry 9). However, notable inhibitory effects were observed with **5j** (entry 10), illustrating that the catalytic amination is sensitive to the type of products generated during the course of reaction. This observation is consistent with our postulate that the progress of amination is affected by the product concentrations with reflection of the substituent's electronic nature.[32]

Kinetic Studies. To describe the kinetic behavior of reactants and catalyst in a catalytic cycle, we performed a series of kinetic experiments under standard conditions. Ellman et al. elucidated that a cationic rhodacycle **10** bearing one molecule of 2-phenylpyridine substrate is a resting species in their Rh-catalyzed imine insertion reaction.[23c] Likewise, because we initially hypothesized that this species may also display a similar kinetic behavior in our C–H amination transformation, we thus decided to use this cationic rhodium species as a catalyst in kinetic study. Prior to kinetic experiments for each substrate, we monitored the progress of amidation by ^1H NMR in a reaction of 2-phenylpyridine (**4a**) with an equimolar ratio of *p*-toluenesulfonyl azide (**2a**) using **10** as a catalyst. Progress in the consumption of **2a** and consequent formation of product **5a** in a 3 h period is depicted in Figure 2.

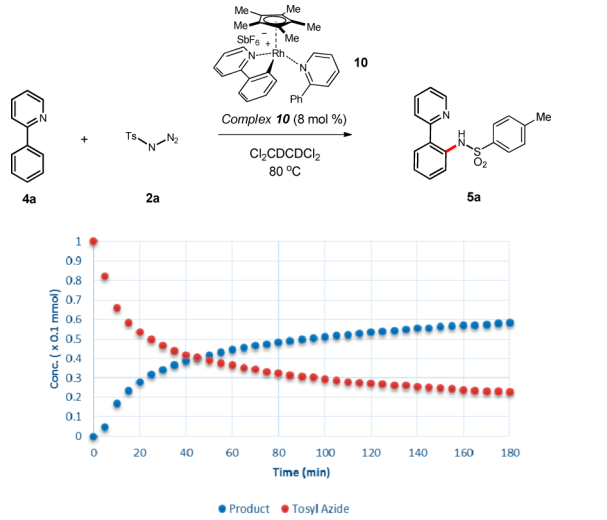


Figure 2. Reaction profile of the Rh-catalyzed amination.

The rate order of each reactant and catalyst in the present amination was determined by the initial-rate method.[33] As shown in Figure 3, rhodium species **10** and *p*-toluenesulfonyl azide (**2a**) were revealed to be the first-order dependence on concentrations (Figure 3a and b, respectively), suggesting that the rhodium catalyst and azide are likely to be involved in the turnover-limiting step. A plot of initial rates of 2-phenylpyridine (**4a**) was also obtained using an analogous procedure to provide an inverse order (Figure 3c). We assume that this result is mainly due to a dual role of 2-phenylpyridine working as a substrate and also as an inhibiting ligand during the course of amination.[23c]

On the basis of our kinetic data, we can simplify the reaction pathway as presented in Scheme 6. Dissociation of 2-phenylpyridine (**4a**) from a cationic rhodium complex (**10**) leaves one vacant site in the metal center leading to **11**, presumably in a reversible manner. The subsequent C–N bond formation will be initiated by the coordination of azide (**2a**) to the unsaturated complex **11** to afford an isolable rhodium amido compound **3a**. Finally, a protodemetalation process will finish the catalytic amination cycle to release the desired product **5a**.

$$\frac{d[\mathbf{11}]}{dt} = 0 = k_1[\mathbf{10}] - (k_{-1}[\mathbf{11}][\mathbf{4a}] + k_2[\mathbf{11}][\mathbf{2a}]) \quad (3)$$

$$[\mathbf{11}] = \frac{k_1[\mathbf{10}]}{k_{-1}[\mathbf{4a}] + k_2[\mathbf{2a}]} \quad (4)$$

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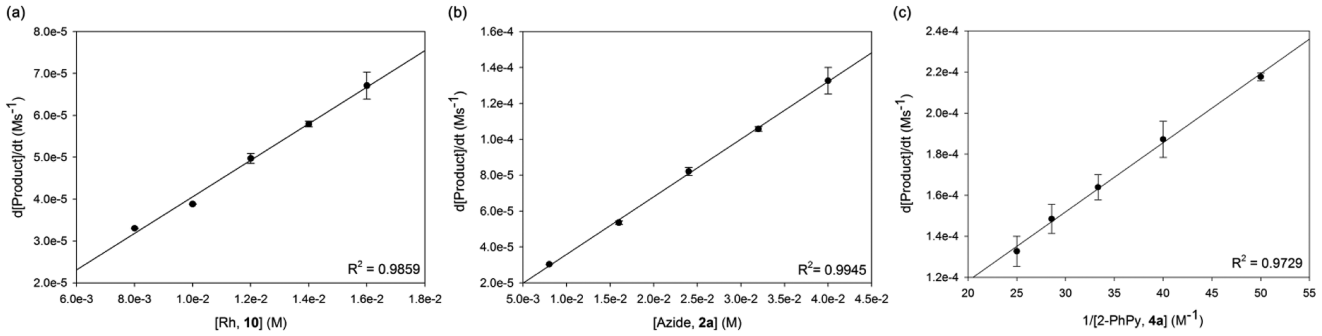
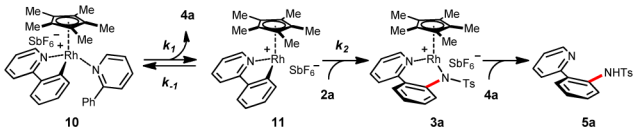


Figure 3. (a) Plot of initial rate versus [**10**] showing the first order. (b) Plot of initial rate versus [**2a**] (*p*-toluenesulfonyl azide) showing the first order. (c) Plot of initial rate versus 1/[**4a**] (2-phenylpyridine) showing the inverse first order.

Scheme 6. Simplified Reaction Pathway



$$-\frac{d[\mathbf{2a}]}{dt} = \frac{d[\mathbf{3a}]}{dt} = k_2[\mathbf{2a}][\mathbf{11}] = \frac{k_1k_2[\mathbf{2a}][\mathbf{10}]}{k_{-1}[\mathbf{4a}] + k_2[\mathbf{2a}]} \quad (5)$$

If $k_{-1}[\mathbf{4a}] \gg k_2[\mathbf{2a}]$:

$$\frac{k_1k_2[\mathbf{2a}][\mathbf{10}]}{k_{-1}[\mathbf{4a}] + k_2[\mathbf{2a}]} \cong \frac{k_1k_2[\mathbf{2a}][\mathbf{10}]}{k_{-1}[\mathbf{4a}]} = k_{obs}\frac{[\mathbf{2a}][\mathbf{10}]}{[\mathbf{4a}]} \quad (6)$$

Assuming a steady-state approximation for **11**, d[**11**]/d*t*, which equals $k_1[\mathbf{10}] - (k_{-1}[\mathbf{11}][\mathbf{4a}] + k_2[\mathbf{11}][\mathbf{2a}])$, can be set as zero (eq 3). Solving this equation for [**11**] leads to $k_1[\mathbf{10}]/(k_{-1}[\mathbf{4a}] + k_2[\mathbf{2a}])$ (eq 4). Insertion of this dependence of [**11**] into an equation (d[**3a**]/d*t*) of the product formation yields a new equation (eq 5) as the amination rate law. In addition, if we assume that $k_{-1}[\mathbf{4a}] \gg k_2[\mathbf{2a}]$, the rate law is simplified as shown in eq 6 that is well described with the obtained kinetic behavior to support our mechanistic interpretation.

To see the electronic influence of azides during the course of the amination reaction, we measured the relative rates in reaction of 2-phenylpyridine (**4a**) with sulfonyl azides bearing *para*-substituents with electronic variation. A Hammett plot of initial rates in a short reaction time provided a linear free energy relationship to indicate that electron-withdrawing substituents retard the amination reaction (Figure 4). Plotting of ln k_{rel} versus σ_p^+ shows the ρ value of ca. −0.66 (R^2 = 0.98)[34] to suggest that the rate-determining transition state is more stabilized by electron-donating substituents.

Computational Studies on the C−N Bond Formation. To investigate the amido insertion process to lead to the C−N bond formation, DFT calculations[35] were performed with B3LYP[36] level using a mixed basis set of Stuttgart relativistic small core effective core potential (SRSC-ECP) basis[37] on rhodium and 6-31G* for other main atoms (Figure 5). Gibbs free energy was corrected by frequency calculations using the optimized structures. Single point solvation energy corrections in 1,2-dichloroethane computed by the ief-PCM method[38,39] were added to the gas-phase free energy. To account for the effect of nonbonding interactions, the solvation-corrected free energies were further corrected by Grimme's DFT-D3 method[40] using a single-point calculation on the gas-phase-optimized structure. Geometry optimization and frequency

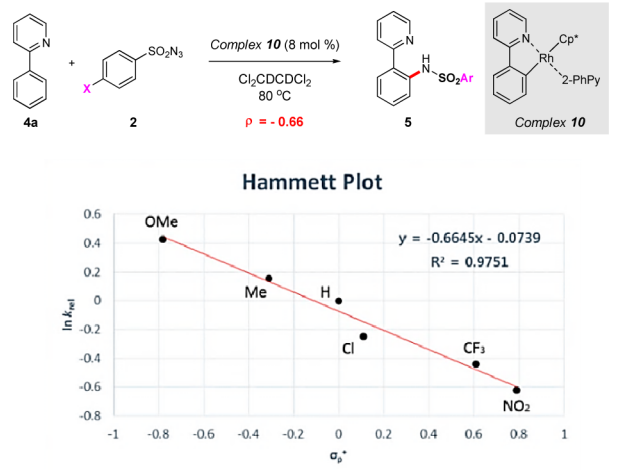


Figure 4. Hammett plot for substituted arenesulfonyl azides.

calculations were performed using the Q-Chem quantum chemistry software.[41] All graphical structures are illustrated using the CYLview program.[42] Because aliphatic sulfonyl azides showed similar reactivity as compared to *p*-toluenesulfonyl azide,[20a] we used methanesulfonyl azide as a model substrate for this theoretical study. On the basis of the above-described experiments, a cationic species [Cp*Rh(III)(2-PhPy)]$^+$ (**11**) was postulated to be formed in this theoretical study by removing a chloride anion by a silver salt from the neutral precursor **1a** followed by coordination of a model substrate (2-phenylpyridine, **4a**) to the unsaturated rhodium metal center. Although the reaction efficiency was observed to be slightly changed depending on the silver additives,[20] noncoordinating counterions derived from the silver salts were not included in the current DFT calculations because the catalytic cycle is operative only by the cationic rhodium metal center. Moreover, we assumed that the overall relative Gibbs free energy surface will not be altered by the presence of noninteracting counteranion spectators as seen in the previous reports.[43]

Dissociation of **4a** from **10** is endergonic by 12.9 kcal/mol, generating a coordinatively unsaturated species **11**. It was interesting to note that the bond length between the rhodium metal center and carbon of a pentamethylcyclopentadienyl (Cp*) ligand is not equivalent depending on the relative position to the 2-phenylpyridyl group. For example, the Rh−C_a distance (2.31 Å) was calculated to be longer than that of Rh−C_b (2.21 Å), presumably due to the discrepancy in the degree of *trans*-influence between the pyridyl and phenyl moieties of the 2-phenylpyridyl ligand in **11** (Figure 6). As a result, this

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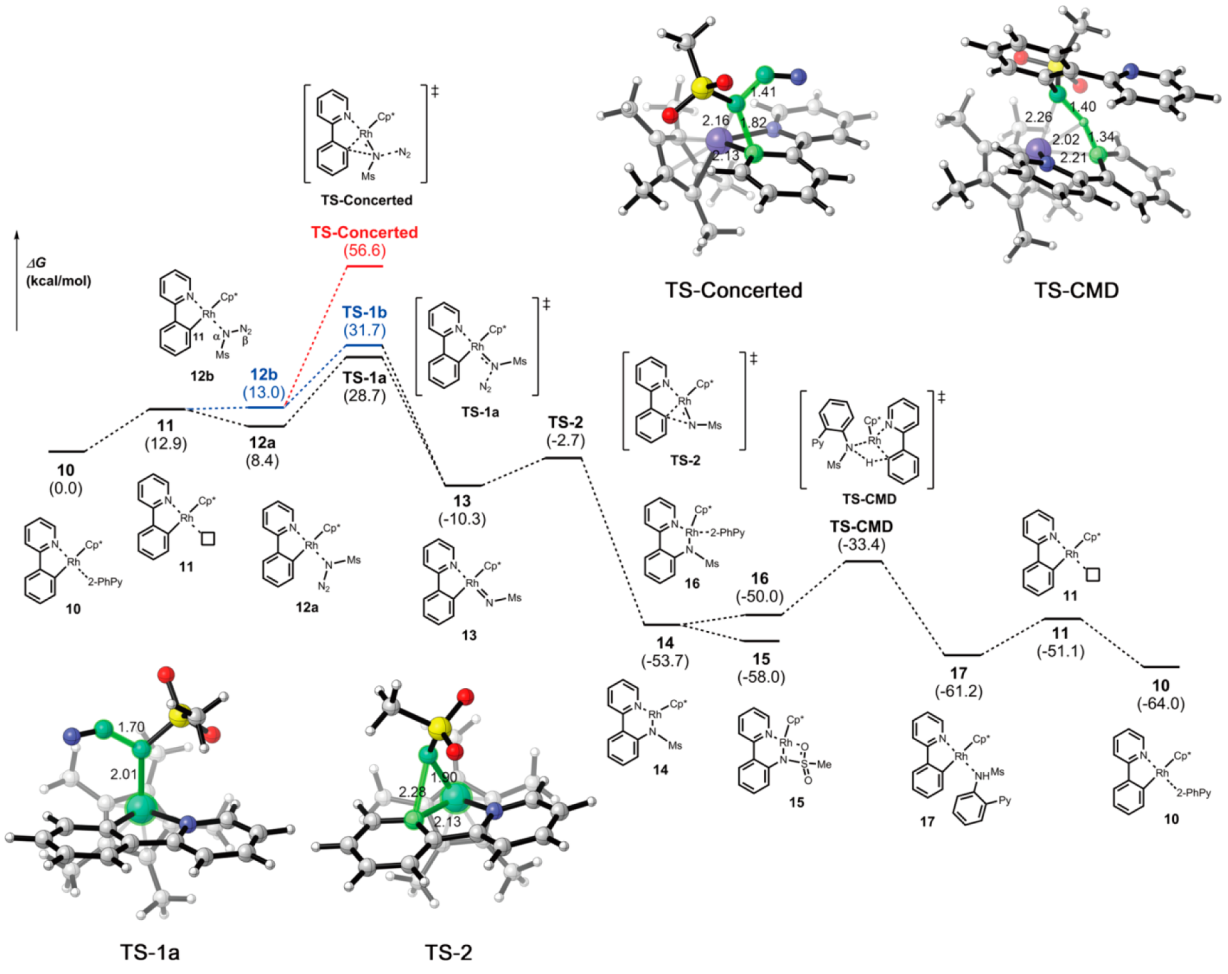

Figure 5. Energy profile of the overall catalytic cycle and 3D structure of selected computed transition states (SbF_6 anion is omitted for clarity). Two pathways from **10** to **14** are differed only by the coordination mode of sulfonyl azide to the rhodium center (black line, sulfonyl group and pyridyl moiety on the same side; blue line, sulfonyl group and pyridyl moiety on opposite sides).

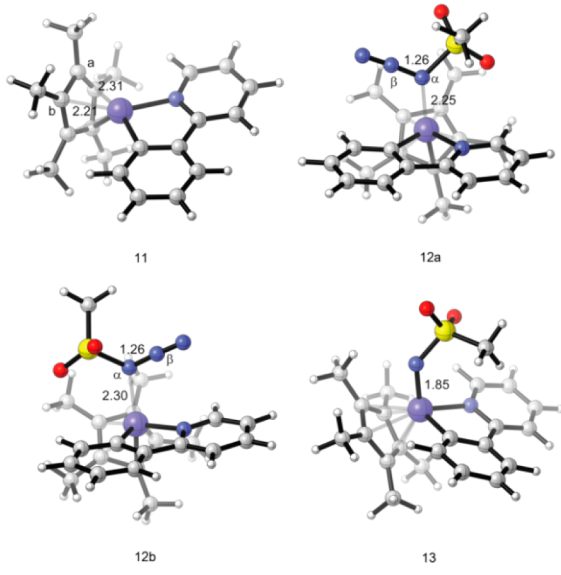

Figure 6. Optimized structures and some bond lengths of selected intermediates in Figure 5.

mode of metal–ligand bonding was revealed to provide more open space around the pyridyl than the phenyl side. Such perturbation results in the directional preference in the coordination of an azide to **11**, making the sterically matched rhodium–azide species **12a** more favorable over **12b** by 4.6 kcal/mol. In addition, the calculated bond elongation between N_α and N_β of a bound azide in **12a** (bond length, 1.26 Å) suggests that π-back-donation occurs slightly from the rhodium metal center to an antibonding orbital of azide. For comparison, the same bond was calculated to be 1.25 Å for unbound methanesulfonyl azide.[26b]

Importantly, DFT calculations allowed us to validate our proposal that the amido insertion process occurs smoothly through a stepwise pathway involving a rhodium nitrenoid intermediate **13**. The activation energy for this exergonic process (**12a** to **13**) was calculated to be 20.3 kcal/mol via a transition state **TS-1a**, leading to a Rh–nitrenoid intermediate **13**. Indeed, this energy barrier lies in the range of previously reported values in the relevant systems involving azide reactants.[44] Because the Rh–nitrogen bond length of an equilibrium structure of **13** was calculated to be 1.85 Å, it can be regarded to have a double bond character. Rh(V)–nitrenoid species **13** subsequently undergoes a reductive amido insertion with a low kinetic barrier (7.6 kcal/mol) passing through a three-centered transition state **TS-2** to give rise to a six-membered Rh(III)–amido species **14** (ΔG = −43.4 kcal/mol). As the last stage of the insertion process, an oxygen atom of the inserted sulfonamido group coordinates to one vacant site of the rhodium metal center in **14** to afford a coordinatively

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saturated species **15**, and this process was calculated to be exergonic by 4.3 kcal/mol. The overall high exothermicity in the insertion pathway (ΔG = −58.0 kcal/mol) is accounted for the generation of a rhodium−nitrenoid species (ΔG = −10.3 kcal/mol) followed by the generation of stable rhodium−amido species **D** (ΔG = −47.7 kcal/mol), and we envisioned that such thermodynamics is a driving force for the catalytic amination.[14e,25b,29b]

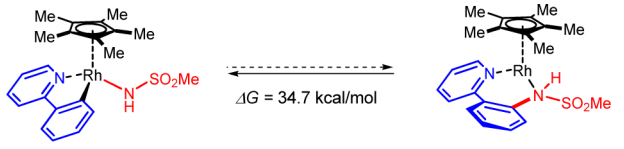
To better understand the oxidation state of the rhodium metal center during the course of the C−N bond-forming step, we performed a Natural Bond Orbital (NBO) analysis.[45] As the rhodium nitrenoid species (**13**) is generated from a cationic rhodacycle **11**, NBO charge on the rhodium center changes from 0.523 to 0.745 to indicate that electron density at the metal center is diminished. Along with this change, the electron binding energy[46] is increased from 89.3 to 90.5 eV (see the Supporting Information, Table S3), thus validating the proposed stepwise pathway, in which the oxidation state of rhodium metal center does change.

On the other hand, we also checked theoretically the feasibility of a concerted pathway for the formation of an amido insertion species **14** starting from an azide coordinated rhodacycle **12b** without involving a discrete rhodium nitrenoid intermediate (**13**). However, our attempts to locate a plausible transition state in the assumed concerted pathway were not successful. In fact, there are examples of metal-mediated amination reactions without involving such nitrenoid species.[47] As a consequence, we performed relaxed potential energy surface scans by gradual changing of the C_{11} and N_α distance in the azide-bound rhodacycle (C_{11} is shown in **12b** in Figure 5).[48] As the N_α atom approaches C_{11} atom, the length of the N_α−N_β bond of azide was shown to be gradually elongated. Eventually, when the distance between C_{11} and N_α reached 1.83 Å, the N_α−N_β bond closed its maximum (1.39 Å). However, intrinsic reaction coordinate (IRC) calculations showed that such geometry is not the proper transition state between **12b** and **14**.

Alternatively, we located a transition state using the M06 functional[49] with structures obtained by relaxed potential energy surface scan as an input structure, and the newly optimized structure was subjected to the single point energy calculation using the B3LYP functional. The resultant structure at this point has a shorter C_{11}−N_α distance (Δd = 0.008 Å) and a longer N_α−N_β distance (Δd = 0.023 Å) as compared to the scanned structure, and, therefore, it can be regarded as a transition state in the concerted pathway, giving a barrier of 43.6 kcal/mol, and this was also confirmed by IRC calculation. When compared to that of the stepwise pathway, this barrier is energetically inaccessible, indeed being much higher than the activation barrier of the overall catalytic reaction (vide infra). It is worth noting that while both NBO charge and electron binding energy were significantly changed in the computed stepwise pathway, change in the concerted pathway was revealed to be negligible, implying that the concerted process is redox-neutral (see the Supporting Information, Table S3). Because the reductive elimination of vicinal ligands is often facilitated by higher oxidation state of metal center, so-called oxidatively induced reductive elimination,[50] we assume that the formation of high valent Rh(V)−nitrenoid species would be critical for the subsequent C−N bond formation.

To see the influence of the oxidation state of metal center on the efficiency in the C−N bond formation, we examined an amido insertion process from a hypothetical Rh(III)−amido species (**18** in Scheme 7) that is analogous to the Rh(V)−nitrenoid **13** in Figure 5. Intriguingly, DFT calculations

Scheme 7. Relative Gibbs Free Energy in a Hypothetical Amido Insertion Process from Rh(III)−Amido Species 18



18, Rh(III) **19**, Rh(I)

revealed that this insertion from Rh(III) is thermodynamically uphill that does not allow the C−N bond formation to afford **19**. In fact, Kakiuchi et al. demonstrated that a low valent ruthenium catalyst can cleave a C−N bond of aryl amines in the arylation of anilines with arylboranes.[51] On the basis of the above experimental and theoretical data as well as precedent literature, we propose that the C−N bond-forming amido insertion process is operative by the intermediacy of a high valent Rh(V)−nitrenoid species.

Coordinatively saturated species **15** can dissociate one oxygen atom of a sulfonamide moiety to give **14** that is then coordinated to 2-phenylpyridine leading to **16** in an endergonic mode. A concerted metalation-deprotonation (CMD) transition state[52] was computed to readily occur through a 2-phenylpyridine-rhodacycle adduct (**16**) with a barrier of 24.6 kcal/mol (**TS-CMD**). Release of an aminated product from **17** occurs as the final step, affording a catalytically active rhodacycle **11**. Total free energy barrier for the rhodium−nitrenoid formation process (from **10** to **13** through **TS-1a**) was calculated to be 28.7 kcal/mol, which is slightly higher than that of the C−H activation step (24.6 kcal/mol, from **15** to **17** through **TS-CMD**). These computational results are fully in accord with our observed kinetic data.

The above theoretical data and experimental kinetic profile of reactants and catalyst indicate that the rate-limiting stage in the current C−H amination reaction would be more closely related to the formation of rhodium−nitrenoid intermediate rather than the presupposed C−H activation step with the concomitant regeneration of an active catalytic species. However, the difference of the activation barrier between those two key processes is not significant according to the DFT calculations. In this regard, we postulated that kinetic isotope studies might provide additional intuitive information. When amination rates were compared between 2-phenylpyridine **4a** and its deuterated analogue **4a**-(d_5) by using a catalytically resting species **10**, the rate difference was observed to be insignificant (k_H/k_D, 1.01; see the Supporting Information for details). The reason for using **10** as a catalyst in this study instead of a precursor $[Cp^*RhCl_2]_2$ was to avoid any complications caused by an induction delay in the conversion of the rhodium dimer to a catalytically resting state. Although it cannot be decisively concluded at the current stage, the KIE data support the above computational description regarding the turnover-limiting step in our direct C−H amination reaction.[53]

Mechanistic Proposal. Our mechanistic proposal on the Rh-catalyzed direct C−H amination reaction is depicted in Scheme 8. It is postulated that the $[Cp^*RhCl_2]_2$ precursor first dissociates to an unsaturated monomer that is subsequently converted to its cationic species by the action of $AgSbF_6$. Because of the highly electrophilic character of the cationic

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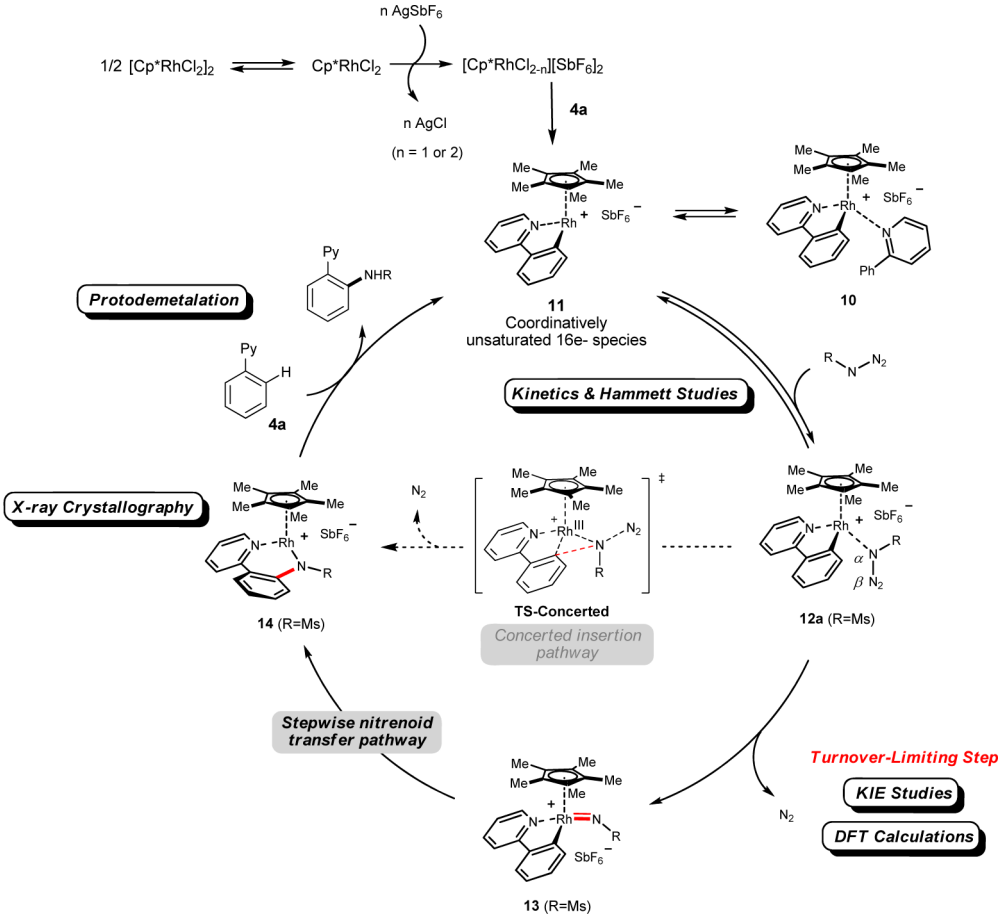
Scheme 8. Mechanistic Proposal of the Rh-Catalyzed Direct C−H Amination



metal center, 2-phenylpyridine substrate can readily coordinate to rhodium followed by the *ortho* C−H bond activation to form a rhodacycle complex **11**. It is assumed that the presence of excessive amounts of substrate (**4a**) leads to a resting state species **10**. Dissociation of a ligand (2-phenylpyridine) from the rhodium center will give back **11**, and then the coordination of an azide molecule is postulated to take place subsequently to give an azide-bound complex **12a**. Insertion of the bound azide into the metallacyclic Rh−C bond will lead to an amido rhodium complex **14** upon release of N_2 presumably through two possible pathways: via a concerted direct insertion or, alternatively, a stepwise pathway involving a rhodium−nitrenoid intermediate.

On the basis of the above experimental and computational studies, we now rule out the concerted pathway that passes through a **TS-Concerted** transition state. Rather, a stepwise route involving a discrete Rh(V)-nitrenoid species (**13**) is proposed to be more plausible. Formation of a rhodium−nitrenoid intermediate from a catalytically resting species **10** is believed to be a rate-limiting step in the overall catalytic cycle. As supported by the experimental results (Table 1) and DFT calculations (Figure 5), protodemetalation of the isolable amido rhodium compounds **14** is assumed to proceed via a concerted metalation−deprotonation (CMD) pathway by using a substrate as a proton source for this process. Finally, an aminated product is released with the concomitant regeneration of Rh(III) species **11** for the subsequent catalytic cycle.

CONCLUSIONS

We have described herein mechanistic details of the Rh(III)-catalyzed direct C−H amination of arenes using organic azides as the nitrogen source. Experimental data and DFT calculations led us to propose that the reaction proceeds via a stepwise pathway involving a Rh(V)−nitrenoid intermediate. The activation barrier of the stepwise pathway was calculated to be energetically feasible. On the other hand, an alternative concerted route for the amide insertion process was shown to be less likely on the basis of the computational studies. While an aminated product is released with the concomitant regeneration of an active rhodacycle catalyst, this final step is proposed to occur through a concerted metalation−deprotonation (CMD) process, in which a substrate works as a proton source. Computational studies and kinetic behavior of each species suggest that the rate-limiting step in the current C−H amination reaction is more closely related to the formation of rhodium−nitrenoid intermediate rather than the presupposed C−H activation stage. Overall, the present study demonstrates that the direct C−H amination reaction provides a new example bearing both aspects of the inner- and outer-sphere paths within a catalytic cycle. On the basis of the mechanistic insights obtained in this study, an additional advance is anticipated in the direct amination reaction, enabling the development of more efficient and selective catalytic systems with broader applicability.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure and characterization of new compounds, including ^{1}H, ^{13}C NMR spectra, Cartesian coordinates of computed structures, 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.

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