C–H Activation

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Rhodium(III)-Catalyzed Activation of C_{sp^3}–H Bonds and Subsequent Intermolecular Amidation at Room Temperature**

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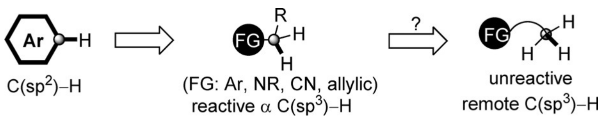
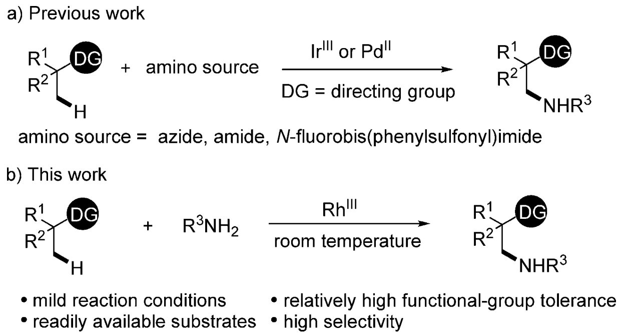
Abstract: *Disclosed herein is a Rh^{III}-catalyzed chelation-assisted activation of unreactive C_{sp^3}–H bonds, thus enabling an intermolecular amidation to provide a practical and step-economic route to 2-(pyridin-2-yl)ethanamine derivatives. Substrates with other N-donor groups are also compatible with the amidation. This protocol proceeds at room temperature, has a relatively broad functional-group tolerance and high selectivity, and demonstrates the potential of rhodium(III) in the promotive functionalization of unreactive C_{sp^3}–H bonds. A rhodacycle having a SbF_6^- counterion was identified as a plausible intermediate.*

Over the past decades, the development of rhodium(III)-catalysis has been an area of intense research in the synthetic organic community. Recently, rhodium(III) has exhibited great potential in the promotion of C_{sp^2}–H bond activation for the construction of carbon–carbon and carbon–heteroatom bonds.[1,2] Undoubtedly, expanding this chemistry to unreactive C_{sp^3}–H sites is an appealing, yet conceptual and practical challenge (Scheme 1). Although a few rhodium-catalyzed functionalizations of reactive C_{sp^3}–H bonds, such as those which are acidic, adjacent to N, allylic, and benzylic have been reported recently,[3] the activation of unreactive and remote C_{sp^3}–H bonds with subsequent functionalization still remains unsolved.[4] Several factors may be responsible for this significant challenge, including: 1) Cleavage of inert, aliphatic C–H bonds with a metal is typically slow because of their high bond strengths; and 2) comprehensive understanding of the mechanistic aspects governing rhodium-catalyzed C_{sp^3}–H activation remains obscure, and thus efficient rhodium catalytic systems are difficult to find. As part of our ongoing efforts in rhodium(III)-catalyzed C–H activation,[5] we herein illustrate a solution to this challenge through a rhodium-catalyzed chelation-assisted amidation of unactivated C_{sp^3}–H bonds as a representative example.



Scheme 1. Evolution of rhodium(III)-catalyzed C–H activation/functionalization.

Recently, the approach toward direct C_{sp^3}–H amination involving a C–H activation process has attracted much attention.[6–8] Despite significant advantages, such as high selectivity and atom efficiency, most of the precedented examples have been restricted to C_{sp^3}–H activation/intramolecular amination,[9] and intermolecular amination was developed initially.[10] Palladium has been established to enable unreactive C_{sp^3}–H bond activation/intermolecular amination.[10a,b] Very recently, Chang and co-workers reported the first iridium-catalyzed ketoxime-assisted intermolecular amidation of unactivated C_{sp^3}–H bonds with azides as the amino source (Scheme 2a).[10c,d] Notably, the majority of the amination reactions require relatively harsh reaction conditions, especially elevated temperatures, which may be incompatible with sensitive functional groups. Thus, it would be valuable to discover an unreactive C_{sp^3}–H bond activation/amination at room temperature.



Scheme 2. Transition-metal-catalyzed activation of unreactive C_{sp^3}–H bonds and subsequent amidation.

2-(Pyridin-2-yl)ethanamine derivatives are important structural motifs widely found in pharmaceuticals and biologically active molecules (Scheme 3).[11] Thus, their synthesis has attracted considerable attention in the organic chemistry community. Conventional routes to 2-(pyridin-2-yl)ethanamine derivatives usually require harsh reaction conditions and multiple-step sequences.[11d,12] Undoubtedly, it would be highly desirable to develop a rapid and concise strategy for the synthesis of these prevalent skeletons. Considering that 2-ethylpyridine derivatives are easily accessible synthetic precursors, we surmised that the selective amination or amida-

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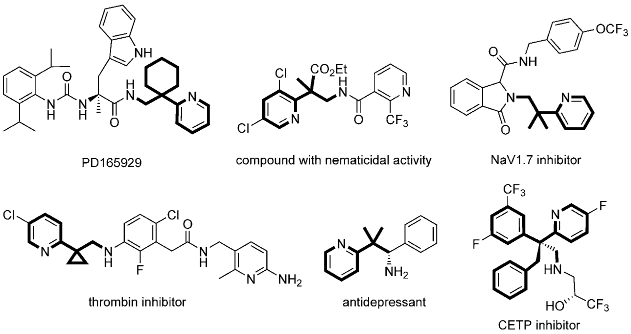


Scheme 3. Selected pharmaceutical and biologically active molecules containing 2-(pyridin-2-yl)ethanamine derivatives.

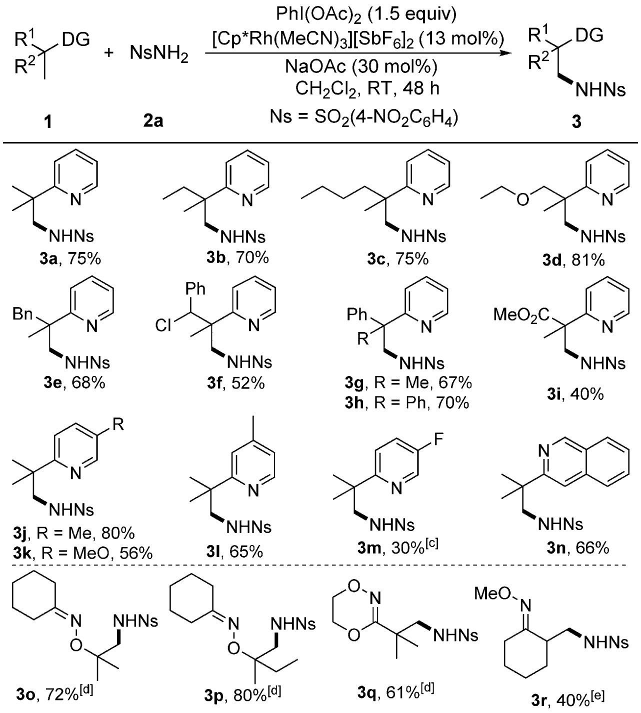
tion of the inert methyl C_{sp^3}–H bond over the relatively activated methylene C_{sp^3}–H bond would offer a practical, step-economic route to 2-(pyridin-2-yl)ethanamine derivatives through the direct use of the inherent pyridyl moiety as the directing group (Scheme 2b).[13]

Our study commenced with the reaction of 2-(*tert*-butyl)pyridine (**1a**) and 4-nitrobenzenesulfonamide (**2a**; for detailed reaction optimization, see Table S1 in the Supporting Information). After screening several parameters (e.g., catalyst, oxidant, additive, solvent, and temperature), **3a** (for structure see Table 1) was obtained in 75% yield with the optimal catalytic system, which comprised $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (13 mol%; Cp* = pentamethyl cyclopentadienyl), $PhI(OAc)_2$ (1.5 equiv), and NaOAc (30 mol%) in CH_2Cl_2 at room temperature for 48 hours. It is worth noting that neither bis(amide) nor tri(amide) compounds were observed when excess **2a** was added (see Table S1, entry 20).

With the optimal reaction conditions in hand, we explored the scope with respect to the 2-ethylpyridine derivatives. As summarized in Table 1, various 2-alkylpyridine derivatives smoothly reacted with **2a**, thus affording the desired products in good yields (**3a–c**). Substrates with functional groups such as alkoxy, phenyl, chloride, and ester on the alkane skeletons were compatible with this reaction (**3d–i**). Moreover, electron-donating substituents on the pyridine ring resulted in satisfactory yields (**3j–l**), whereas an electron-withdrawing substituent disfavored the amidation (**3m**). When isoquinoline was used as a directing group, the amidated product was obtained in 66% yield (**3n**). Other kinds of alkanes with different N-donor groups were also investigated. Cyclohexane ketoximes, derived from tertiary alcohols, were compatible with this amidation reaction in satisfactory yields (**3o** and **3p**). 3-(*tert*-Butyl)-5,6-dihydro-1,4,2-dioxazine reacted with **2a** to give the amidated product **3q** in 61% yield. Moreover, (*E*)-2-methylcyclohexanone *O*-methyl oxime could undergo β-amidation of a primary C_{sp^3}–H bond (**3r**).

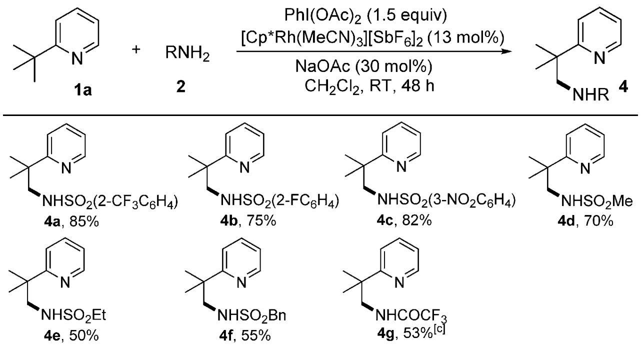
Next, investigation of scope with respect to the amide revealed that other aryl sulfonamides possessing an electron-withdrawing group on the phenyl ring had similar reactivity (**4a–c**; Table 2). Alkyl sulfonamides could also undergo the amidation process in acceptable yields (**4d–f**). With an excess of 2,2,2-trifluoroacetamide, 2-(*tert*-butyl)pyridine was transformed into the amidated product **4g** in 53% yield.

Table 1: The scope with respect to the alkanes having different directing groups.[a,b]



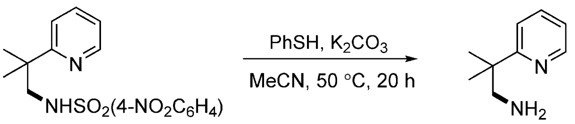
[a] Reactions were performed with **1** (0.50 mmol) and **2a** (0.25 mmol) in 0.75 mL of CH_2Cl_2. [b] Yields of isolated products. [c] $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (20 mol%), 72 h. [d] $[\{RhCp^*Cl_2\}_2]$ (8.0 mol%), $AgNTf_2$ (32 mol%), and CH_2Cl_2 (0.5 mL). [e] $[\{RhCp^*Cl_2\}_2]$ (12 mol%), $AgNTf_2$ (48 mol%), and CH_2Cl_2 (0.5 mL), 72 h. Tf = trifluoromethanesulfonyl.

Table 2: The scope with respect to the amides.[a,b]

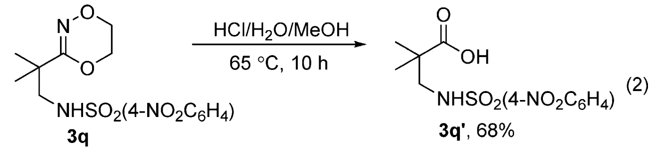


[a] Reactions were performed with **1a** (0.50 mmol) and **2** (0.25 mmol) in 0.75 mL of CH_2Cl_2. [b] Yields of isolated products. [c] **1a** (0.25 mmol) and 2,2,2-trifluoroacetamide **2l** (0.5 mmol).

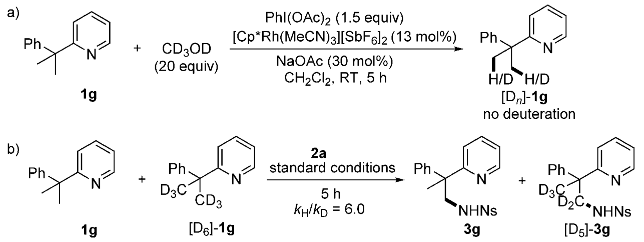
By using PhSH and K_2CO_3 in MeCN, **3a** was deprotected to give 2-methyl-2-(pyridin-2-yl)propan-1-amine (**5**) in 90% yield [Eq. (1)].[14] The amidated product **3q** could also be conveniently transformed into a β-amino acid in 68% yield [Eq. (2)].[15]



3a **5**, 90% (1)

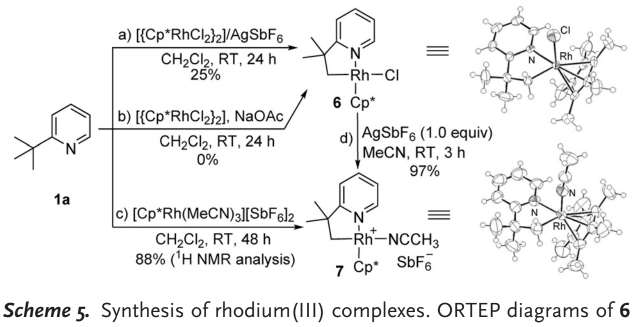


To gain insight into the reaction mechanism, deuterium-labeling experiments were conducted. The hydrogen–deuterium exchange experiments exhibited that the primary C_{sp^3}–H bond cleavage was an irreversible process (Scheme 4a). The intermolecular competition reaction between **1g** and [D$_6$]-**1g** with **2a** in one vessel gave a notable primary kinetic isotopic effect ($k_H/k_D = 6.0$; Scheme 4b). This result revealed that the C–H bond cleavage might be related to the rate-determining step.[16]



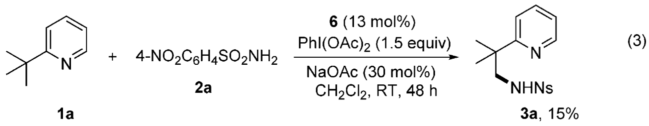
Scheme 4. Deuterium-labeling experiments.

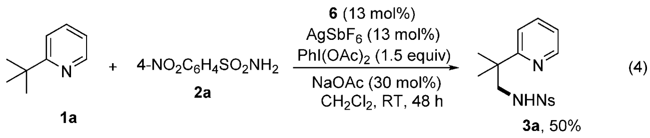
As the *tert*-butyl group has a conformational bias to favor of the formation of cyclometalated species, **1a** was used to isolate rhodacycle intermediates. Surprisingly, **1a** reacted stoichiometrically with [{RhCp*Cl$_2$}$_2$] and AgSbF$_6$ to afford the neutral rhodium(III) complex **6** (Scheme 5a). Usually, the rhodacycle formation reactions in the presence of [{RhCp*Cl$_2$}$_2$]/AgSbF$_6$ would give the corresponding cationic five-membered rhodacycle complex with the SbF_6^- counterion as a noncoordinating anion.[17] It is notable that **6** could not be obtained without AgSbF$_6$ (Scheme 5b). When **1a** reacted with [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$, the cationic rhodium species **7** could be obtained in an excellent yield (Scheme 5c). Moreover, the neutral complex **6** could also be transformed into **7** by using a stoichiometric amount of AgSbF$_6$ to remove chloride (Scheme 5d). The structures of the complexes **6** and **7** were confirmed by X-ray crystallographic analysis.[18]

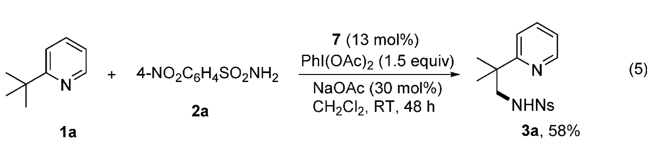


Scheme 5. Synthesis of rhodium(III) complexes. ORTEP diagrams of **6** and **7**. The SbF_6^- counterion of **7** in the ORTEP diagram is omitted. Thermal ellipsoids are shown at 50% probability.

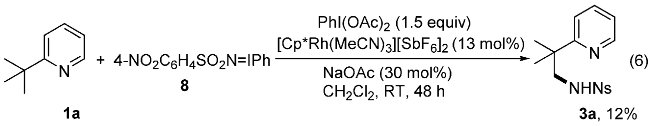
The amidation reaction of **1a** with **2a** by using neutral **6** as the catalyst furnished the desired product **3a** in only 15% yield [Eq. (3)]. However, the yield of **3a** increased to 50% when AgSbF$_6$ was introduced into the reaction mixture [Eq. (4)]. Moreover, **7** also catalyzed the amidation of **1a** to afford **3a** in 58% yield [Eq. (5)]. These results suggested the possible intermediacy of a cationic five-membered rhodacycle complex in the catalytic cycle.

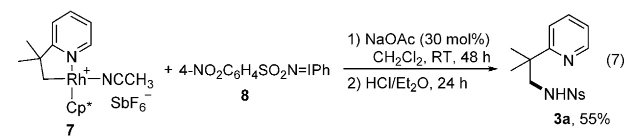




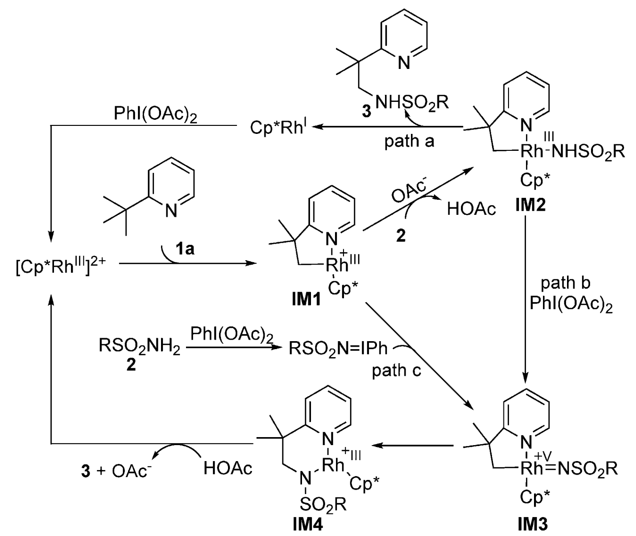


Given that a nitrene precursor might be generated in situ from PhI(OAc)$_2$ and sulfonamide, two experiments were performed to confirm whether a nitrene intermediate was involved in the catalytic cycle. The reaction of **1a** with the nitrene precursor **8**[19] gave **3a** in 12% yield [Eq. (6)]. A further experiment afforded **3a** in 55% yield by using **7** and **8** as substrates [Eq. (7)]. The facts imply that a nitrene intermediate is likely involved in the amidation process.





Based on the above investigations and known rhodium(III)-catalyzed C–H bond functionalizations,[2,3d,20] a plausible mechanistic pathway is proposed (Scheme 6). First, the intermediate **IM1** is generated through chelation-assisted C_{sp^3}–H activation. Next, the reaction has three possible paths.[20] In path a, **IM1** reacts with a sulfamide to produce the intermediate **IM2**. After sequential reductive elimination and reoxidation of the [Cp*Rh^{I}] species, the desired product is obtained and [Cp*Rh^{III}] is regenerated. In the other cases, **IM2** could be oxidized by PhI(OAc)$_2$ to afford a rhodium(V) nitrenoid intermediate (**IM3**; path b), which could also be obtained from the reaction of **IM1** with a nitrene precursor generated in situ from PhI(OAc)$_2$ and the sulfonamide **2** (path c). Subsequently, the sulfonamido unit inserts into the



Scheme 6. Plausible mechanistic pathway.

C–Rh bond to form the intermediate **IM4**. Finally, protonolysis of **IM4** gives the coupled product **3**.

In summary, we have developed a rhodium(III)-catalyzed chelation-assisted amidation of unactivated C_{sp^3}–H bonds by using amides as the amino source at room temperature, thus showing that rhodium(III) can activate unreactive, aliphatic C–H bonds under mild reaction conditions. Various substrates containing inert C_{sp^3}–H bonds smoothly undergo this coupling process with relatively broad functional-group tolerance and complete monoselectivity. A cationic five-membered rhodacycle complex has been established as a possible intermediate. We believe that this strategy represents an efficient route to 2-(pyridin-2-yl)ethanamine derivatives for medical and natural product chemistry studies.

Keywords: C–H activation · heterocycles · rhodium · sulfonamides · X-ray diffraction

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