Rhodium(III)-Catalyzed Intermolecular N-Chelator-Directed Aromatic C—H Amidation with Amides

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Received August 28, 2013

ABSTRACT



Rh(III)-catalyzed intermolecular direct aromatic C–H bond amidation with amides has been accomplished under mild reaction conditions. This protocol is applicable to a broad range of N-chelator-containing arenes amidated with aromatic and aliphatic sulfonamides. A possible mechanism is proposed according to the experimental results.

Although the Buchwald–Hartwig amination reactions¹ and the Ullmann-Goldberg coupling reactions² have provided powerful tools for the syntheses of aryl amines, the ubiquity of (hetero)aryl-nitrogen bonds in natural products, pharmaceuticals, agrochemicals, and organic materials³ continues to be the great impetus to the development of efficient methods for constructing (hetero)aryl-nitrogen bonds. From the standpoint of atom- and step-economy, transition-metal catalyzed direct C-H amination with amines or amides would be the ideal approach to aryl amines or N-arylated amides. However, the achievement of direct C-H amination starting from amines or amides represents a challenging goal because of the coordination of amines or amides to catalyst centers that may lead to catalyst poisoning or a decrease in catalytic activity for C-H activation, and the lack of stability of certain amines under oxidative conditions. A strategy to effect the direct amination of (hetero)arenes is the use of the amino or amido precursors such as oxime derivatives,⁴ chloroamines,⁵ *N*-fluorobenzenesulfonimide,⁶ and azides.⁷ Recently, much effort has been made to achieve the direct C–H amination of (hetero)arenes with amines or amides, successfully establishing some methods that enable the use of amines or amides for the amination of C–H bonds,⁸ and the groups of Yu and Che have contributed to the pioneering work.^{9a} Despite these advances, intermolecular C–H amination with amines or amides is still limited to specific substrates.⁹

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 ^{(1) (}a) Paul, F.; Patt, J.; Hartwig, J. F. J. Am. Chem. Soc. 1994, 116, 5969. (b) Guram, A. S.; Buchwald, S. L. J. Am. Chem. Soc. 1994, 116, 7901.

⁽²⁾ Evano, G.; Blanchard, N.; Toumi, M. Chem. Rev. 2008, 108, 3054.
(3) (a) Ricci, A. Amino Group Chemistry: From Synthesis to the Life Sciences; Wiley-VCH: Weinheim, 2008. (b) Hili, R.; Yudin, A. K. Nat. Chem. Biol. 2006, 2, 284. (c) Boaen, N. K.; Hillmyer, M. A. Chem. Soc. Rev. 2005, 34, 267.

^{(4) (}a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. J. Am. Chem. Soc. 2010, 132, 12862. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. J. Am. Chem. Soc. 2011, 133, 7652. (c) Matsuda, N.; Hiranoo, K.; Stoh, T.; Miura, M. Org. Lett. 2011, 13, 2860. (d) Grohman, C.; Wang, H.; Glorius, F. Org. Lett. 2013, 15, 3014. (e) Yu, S.; Wan, B.; Li, X. Org. Lett. 2013, 15, 3706.

^{(5) (}a) Kawano, T.; Hiranoo, K.; Satoh, T.; Miura, M. J. Am. Chem. Soc. 2010, 132, 6900. (b) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. Org. Lett. 2012, 14, 272. (c) Grohmann, C.; Wang, H.; Glorius, F. Org. Lett. 2012, 14, 656.

^{(6) (}a) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. J. Am. Chem. Soc. 2011, 133, 1694. (b) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. Adv. Synth. Catal. 2013, 355, 869.

^{(7) (}a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. J. Am. Chem. Soc. 2007, 129, 7500. (b) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. J. Am. Chem. Soc. 2012, 134, 9110.
(c) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. Angew. Chem., Int. Ed. 2013, 52, 8301. (e) Kim, J.; Kim, J.; Chang, S. Angew. Chem., Int. Ed. 2013, 52, 8301. (e) Kim, J.; Kim, J.; Chang, S. Chem.—Eur. J. 2013, 19, 7328. (f) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. Org. Lett. 2013, 15, 1638. (g) Zheng, Q.-Z.; Liang, Y.-F.; Qin, C.; Jiao, N. Chem. Commun. 2013, 49, 5654. (h) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Achermann, L. Org. Lett. 2013, 15, 3286.

⁽⁸⁾ For selected reviews on C–H amination/amidation, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (e) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.

Recently, the Rh(III) catalyst for C–H functionalization has attracted more attention due to its high catalytic activity and excellent functional group tolerance.^{10,11} In the context of C–H amination, the Rh catalyst proved to be very efficient for the transformation of allylic, benzylic, and certain unactivated sp³ C–H bonds.^{8b,12} These elegant studies led us to consider whether a Rh catalyst is applicable to the direct amination of aromatic C–H bonds with amines or amides. Herein, we describe a mild, efficient Rh(III)-catalyzed method for N-chelator-directed *ortho* sp² C–H bond amidation with sulfonamides.

Recent advances in the Rh(III)-catalyzed C–H bond activation^{10,11} have afforded valuable starting points for our exploration in the direct amidation of arenes with sulfonamides. We selected the reaction of 2-phenylpyridine (**1a**) and *p*-toluenesulfonamide (**2a**) as the model reaction. The [Cp*Rh(III)](SbF₆)₂, which can be generated *in situ* from [Cp*RhCl₂]₂ in the presence of AgSbF₆, was selected as the catalyst. Initially, the model reaction that was performed at 100 °C using Ag₂CO₃ as the oxidant in the presence of 5 mol % of Rh(III) only generated a small amount of the desired product **3a**, in CH₂Cl₂ (Table 1, entry 4). No desired product was obtained when the

(10) For selected reviews on Rh(III)-catalyzed C-H activations, see:
(a) Satoh, T.; Miura, M. Chem.—Eur. J 2010, 16, 11212. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. 2012, 45, 814. (c) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. Aldrichimica Acta 2012, 45, 31. (d) Song, G.; Wang, F.; Li, X. Chem. Soc. Rev. 2012, 41, 3651.

(11) For selected examples of Rh(III)-catalyzed C-H activations, see: (a) Guimond, N.; Gouliaras, C.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 6908. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. J. Am. Chem. Soc. 2011, 133, 2350. (c) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. 2011, 133, 1248. (d) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. Angew. Chem., Int. Ed. 2011, 50, 2115. (e) Wencel-Delord, J.; Mimphius, C.; Patureau, F. W.; Glorius, F. Angew. Chem., Int. Ed. 2012, 51, 2247. (f) Schröder, N.; Wencel-Delord, J.; Glorius, F. J. Am. Chem. Soc. 2012, 134, 8298. (g) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. J. Am. Chem. Soc. 2012, 134, 19592. (h) Morimoto, K.; Itoh, M.; Hirano, K.; Satoh, T.; Shibata, Y.; Tanaka, K.; Miura, M. Angew. Chem., Int. Ed. 2012, 51, 5359. (i) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. Science 2012, 338, 500. (j) Ye, B.; Cramer, N. Science 2012, 338, 504. (k) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. J. Am. Chem. Soc. 2012, 134, 13565. (l) Zhen, W.; Wang, F.; Zhao, M.; Du, Z.; Li, X. Angew. Chem., Int. Ed. 2012, 51, 11819. (m) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. Angew. Chem., Int. Ed. 2012, 51, 3948. (n) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. Angew. Chem., Int. Ed. 2013, 52, 580. (o) Neely, J. M.; Rovis, T. J. Am. Chem. Soc. 2013, 135, 66. (p) Wang, H.; Schröder, N.; Glorius, F. Angew. Chem., Int. Ed. 2013, 52, 5386. (q) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. J. Am. Chem. Soc. 2013, 135, 8850.

(12) (a) Zalatan, D. N.; Bios, J. D. In *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z.-J., Eds.; Springer: Berlin, 2010; Vol. 292, pp 364–370. (b) Bois, J. D. Org. Process Res. Dev. **2011**, *15*, 758.



Table 1. Optimization of the Rh-Catalyzed Amidation^a

| entry | oxidant (equiv) | solvent | temp (°C) | yield (%) ^b |
|----------|--|--------------------------------------|--------------|---------------------------|
| 1 | $Ag_2CO_3(2.0)$ | DMSO | 100 | 0 |
| 2 | $Ag_2CO_3(2.0)$ | DMF | 100 | 0 |
| 3 | $Ag_2CO_3(2.0)$ | 1,4-dioxane | 100 | 0 |
| 4 | $Ag_2CO_3(2.0)$ | CH_2Cl_2 | 100 | 5 |
| 5 | $Ag_2CO_3(2.0)$ | toluene | 100 | 20 |
| 6 | AgOAc (4.0) | toluene | 100 | 5 |
| 7 | $Cu(OAc)_2(2.0)$ | toluene | 100 | 5 |
| 8 | $PhI(OAc)_{2}(2.0)$ | toluene | 100 | 20 |
| 9 | $PhI(OAc)_{2}(2.0)$ | CH_2Cl_2 | 100 | 60 |
| 10 | $PhI(OAc)_{2}(1.5)$ | CH_2Cl_2 | 100 | 74 |
| 11 | $PhI(OAc)_{2}(1.5)$ | CH_2Cl_2 | 80 | 74 |
| 12 | PhI(OAc) ₂ (1.5) | CH_2Cl_2 | 60 | 76 |
| 13 | $PhI(OAc)_2(1.5)$ | CH_2Cl_2 | 40 | 71 |
| 14 | PhI(TFA) ₂ (1.5) | CH_2Cl_2 | 60 | 0 |
| 15 | PhI(OCO ^{t-} Bu) ₂ | CH_2Cl_2 | 60 | 58 |
| | (1.5) | | | |
| 16 | $PhI(OAc)_{2}(1.5)$ | ClCH ₂ CH ₂ Cl | 60 | 59 |
| 17^c | $PhI(OAc)_{2}(1.5)$ | CH_2Cl_2 | 60 | 54 |
| 18^d | $PhI(OAc)_{2}(1.5)$ | CH_2Cl_2 | 60 | 69 |
| 19^e | $PhI(OAc)_2(1.5)$ | CH_2Cl_2 | 60 | 0 |
| 20^{f} | $PhI(OAc)_2(1.5)$ | CH_2Cl_2 | 60 | 62 |

^{*a*} Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $[Cp*RhCl_{2]_2}$ (2.5 mol %), AgSbF₆ (10 mol %), oxidant, solvent (2 mL), 24 h. ^{*b*} Isolated yield. ^{*c*} In absence of AgSbF₆. ^{*d*} **1a** (0.2 mmol), **2a** (0.4 mmol). ^{*e*} In absence of $[Cp*RhCl_{2]_2}$. ^{*f*} **1a** (0.2 mmol), **2a** (0.2 mmol); **3a** was the only product, and a diamidated product was not observed.

reaction was carried out in other solvents, such as DMSO, DMF, and 1,4-dioxane (entries 1-3). When toluene was used as the solvent, the yield of the transformation reached 20% (entry 5). We further tested other oxidants including inorganic and organic compounds (entries 6-8) and found that the effect of soluble PhI(OAc)₂ was similar to that of Ag₂CO₃ (entry 8). Satisfactorily, the change of solvent to CH₂Cl₂ led to **3a** in 60% yield (entry 9). Further investigations revealed that the reaction could occur under a milder temperature (60 °C) with the improved yield (entries 10-13). Other hypervalent iodide (III) reagents with different anions were inferior to PhI(OAc)₂ (entries 14 and 15), which presumably resulted from the effects of the different anions generated from iodide reagents on C-H bond activation.¹³ A control experiment showed that the Rh catalyst was necessary for the reaction to occur (entry 19).

Using the optimized condition (Table 1, entry 12), we first evaluated the substrate scope of arenes. As shown in Scheme 1, the 2-arylpyridines containing electron-donating groups such as a methyl or methoxy substituent in the

⁽⁹⁾ For the transition-metal catalyzed the amination/amidation of (hetero)arenes with amines/amides, see: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. J. Am. Chem. Soc. 2006, 128, 9048. (b) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. J. Am. Chem. Soc. 2011, 133, 1466. (c) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. J. Am. Chem. Soc. 2013, 135, 8480. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. J. Am. Chem. Soc. 2006, 128, 6790. (e) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. Org. Lett. 2009, 11, 1607. (f) Wang, Q.; Schreiber, S. L. Org. Lett. 2009, 11, 5178. (g) Zhao, H.; Wang, M.; Su, W.; Hong, M. Adv. Synth. Catal. 2010, 352, 1301. (h) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. Org. Lett. 2011, 13, 359. (i) John, A.; Nicholas, K. M. J. Org. Chem. 2011, 76, 4158. (j) Tran, L. D.; Roane, J.; Daugulis, O. Angew. Chem., Int. Ed. 2013, 325, 1315. (l) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. Angew. Chem., Int. Ed. 2009, 48, 9127. (m) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. Angew. Chem., Int. Ed. 2010, 49, 9899.

^{(13) (}a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. J. Am. Chem. Soc. 2005, 127, 13754. (b) Lafrance, M.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 16496. (c) Li, L.; Brennessel, W. W.; Jones, W. D. Organometallics 2009, 28, 3492.

para or meta positions on the aryl moiety were efficiently coupled with the amide, producing the desired products with good yields (3b, 3c, 3g, and 3h). However, the substituent on the 2-position of the aromatic ring resulted in a slightly lower yield probably due to the steric factor (3g). Substrates bearing an electron-withdrawing group afforded an excellent yield (3d). Notably, the aldehyde and bromide groups, which are versatile for chemical transformations, were also tolerated (3e and 3f). We next examined the substituent effect of the pyridine moiety. Methyl and fluoro substituents on the 5'-position of pyridine furnished the desired products in 74% and 71% yields (3i and 3i). The amidations of 1-phenylisoquinoline and benzo-[h]quinoline afforded the desired products, 3k and 3l, in 70% and 91% yields. Interestingly, the optimal conditions are also applicable to other heterocycles besides pyridine. Amidation of 1-phenylpyrazole afforded the desired product (3m) in 62% yield. We also found that any oxazolines underwent smoothly the amidation at the ortho-position, affording the corresponding products (3n-3q) in good to excellent yields at the elevated temperature (100 °C).





^{*a*} Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $[Cp*RhCl_2]_2$ (2.5 mol %), AgSbF₆ (10 mol %), PhI(OAc)₂ (0.3 mmol), CH₂Cl₂ (2 mL), isolated yield. ^{*b*} Reactions were performed at 100 °C.

Additionally, the scope of sulfonamides was examined under the established conditions (Scheme 2). The sulfonamides containing electron-withdrawing groups such as F, Cl, Br, CF₃, or NO₂ on the arene moiety furnished good yields (4d-4j) while arylsulfoamide substrates bearing electron-donating groups such as methyl (4b) or methoxy (4c) resulted in slightly diminished yields. By increasing the reaction temperature to 100 °C, alkyl-substituted sulfonamides also reacted efficiently (4l-4n). It is worth mentioning that the methodology could also be applied to electron-deficient amide (40). Unfortunately, some amides such as *N*-methyl arylsulfonamides, benzamides, and anilines did not react with the arenes under the optimal or modified reaction conditions. We speculate that the amines bearing strong electron-withdrawing groups can increase the acidity of the N-H bond and assist the amides to couple with arenes.





^{*a*} Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $[Cp*RhCl_2]_2$ (2.5 mol %), AgSbF₆ (10 mol %), PhI(OAc)₂ (0.3 mmol), CH₂Cl₂ (2 mL). ^{*b*} Reactions were performed at 100 °C. ^{*c*} **1a** (0.2 mmol), **2** (1.1 equiv).

To obtain some preliminary mechanistic insight into the amidation reaction, we performed isotope labeling experiments (Scheme 3). When CD₃OD was added as the mixed solvent, a significant H/D scrambling exclusively in the *ortho*-position of the phenyl group was observed (Scheme 3a). On top of that, the intermolecular competition experiment between 2-phenylpyridine and 2-(pentadeuteriophenyl)pyridine in one vessel was not indicative of a notable primary kinetic isotope effect ($k_{H/D} =$ 1.67) (Scheme 3b).¹⁴ These data suggested that the Rhcatalyzed *ortho*-C–H bond cleavage in the amidation reaction is reversible.

Presynthesized cyclometalated Rh(III) complex 5^{15} reacted with sulfonamide (2a) producing the amidating product in 50% yield (Scheme 4a). We also observed that complex 5 could catalyze the amidation of the C–H bond and furnished the desired product in 74% yield (Scheme 4b). These reactions indicate that 5 is a plausible activated intermediate in the reaction. To identify whether

⁽¹⁴⁾ Simmons, E. M.; Hartwig, J. F. Angew. Chem., Int. Ed. 2012, 51, 3066.

⁽¹⁵⁾ Li, L.; Brennessel, W. W.; Jones, W. D. J. Am. Chem. Soc. 2008, 130, 12414.

Scheme 3. Deuteration Experiments



a nitrene intermediate (PhI=N-Ts, 6) is generated from the reaction of PhI(OAc)₂ with sulfonamide, the reaction of nitrene precursor 6 was carried out under identical conditions (Scheme 4c), which afforded only an $\sim 10\%$ yield of the product. A further experiment (Scheme 4d) gave the desired product in 56% yield. These results suggested that the Rh-catalyzed C-H amidation likely involved the nitrene intermediate.

Scheme 4. Mechanistic Experiments



Based on the experiments and related Rh-catalyzed C–N bond formation reported by others,^{4d,7c,7d} a plausible mechanism for this reaction is proposed in Scheme 5. A highly electrophilic Rh(III) species I is generated from the Rh precursor, which is stabilized by coordinating to the nitrogen of 2-phenylpyridine. The N-directed C–H bond activation occurs via a base-assisted concerted metalation–deprotonation process,^{11e,13c} forming a five-membered-rhodacycle III.^{11c,d} Subsequently, the reaction may proceed via three possible paths. In the case of *path a*, the

amide transfers to the Rh(III) center with the aid of a base, yielding the intermediate **IV** that undergoes reductive elimination to form the C–N bond and Rh(I) intermediate **VI**. Then, the Rh(I) intermediate is oxidized by PhI(OAc)₂ to generate Rh(III) intermediate **VII**. In *path* b and c, the intermediate nitrenoid **V**¹⁶ possessing a Rh(V) center^{11e,f,17} is generated via the intermediate **IV** or **III**, respectively. The intermediate **V** undergoes reductive elimination to form C–N bond Rh(III) species **VII**. Finally, the sixmembered rhodacycle is protonated by the acid generated *in situ*, producing the desired product.

Scheme 5. Proposed Mechanism



In summary, a novel Rh-catalyzed method for the N-chelator directed *ortho*-sp² C–H bond amidation has been developed for the first time, which allowed using sulfonamides as the amidating reagents under mild reaction conditions. This efficient method enables various arenes to be amidated with both aromatic and aliphatic sulfonamides with good functional group tolerance and selectivity in good to excellent yields, providing a complement to the existing amidation methods. Our future work is to expand the substrate scope of this protocol and get a better understanding of the reaction mechanism.

Acknowledgment. Financial support from the 973 Program (2011CB932404, 2011CBA00501), NSFC (20925102, 21202164), and National Key Technology R & D Program (2012 BAE 06B08) is greatly appreciated.

Supporting Information Available. Detailed experimental procedures and characterization for products. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹⁶⁾ For Rh(V)-nitrenoid species, see: Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. J. Org. Chem. **2012**, *77*, 3017.

⁽¹⁷⁾ For Rh(V) species, see: (a) Duckett, S. B.; Perutz, R. N. Organometallics 1992, 11, 90. (b) Brayshaw, S. K.; Sceats, E. L.; Green, J. C.; Weller, A. S. Proc. Natl. Acad. Sci. U.S.A. 2007, 104, 6921. (c) Vyboishchikov, S. F.; Nikonov, G. I. Organometallics 2007, 26, 4160.

The authors declare no competing financial interest.