

# Rhodium-Catalyzed NH Insertion of Pyridyl Carbenes Derived from Pyridotriazoles: A General and Efficient Approach to 2-Picolylamines and Imidazo[1,5-*a*]pyridines\*\*

Yi Shi, Anton V. Gulevich, and Vladimir Gevorgyan\*

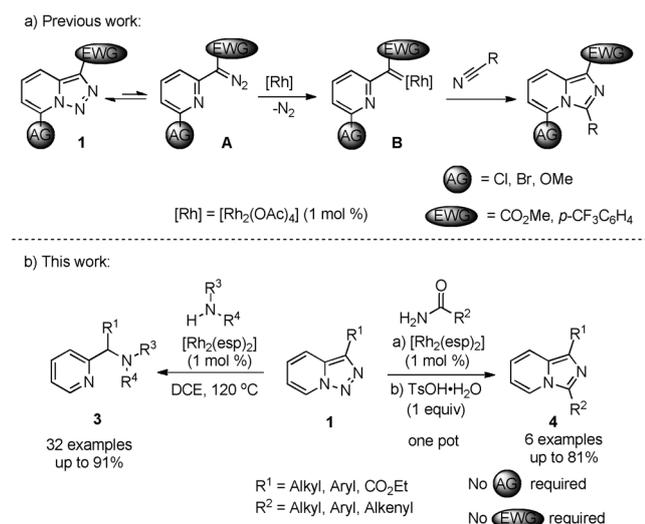
**Abstract:** A general and efficient NH insertion reaction of rhodium pyridyl carbenes derived from pyridotriazoles was developed. Various NH-containing compounds, including amides, anilines, enamines, and aliphatic amines, smoothly underwent the NH insertion reaction to afford 2-picolylamine derivatives. The developed transformation was further utilized in a facile one-pot synthesis of imidazo[1,5-*a*]pyridines.

**T**ransition-metal-catalyzed denitrogenative transannulation of pyridotriazoles<sup>[1]</sup> is a powerful method for the synthesis of nitrogen-containing heterocycles.<sup>[2–4]</sup> As a convenient progenitor of metal carbene species, the pyridotriazole **1** exists in equilibrium with the diazo form **A**, which can be trapped with rhodium(II) to form the reactive pyridyl carbene intermediate **B** (Scheme 1 a). In 2007, our group reported the trans-

annulation reaction of pyridotriazoles based on the reaction of **B** with nitriles. It was shown that Cl, Br, or OMe substituents at C7 (AG = activating group), as well as electron-withdrawing (EWG) groups at C3, were requisite for efficient formation of the imidazo[1,5-*a*]pyridines (Scheme 1 a).<sup>[1a]</sup> Naturally, we were interested in expanding the scope of imidazo[1,5-*a*]pyridines which can be accessed by transannulation reaction of pyridotriazoles. Herein, we report a general rhodium-catalyzed NH insertion reaction of **B**, derived from **1**, to afford the valuable picolylamine derivatives **3** (Scheme 1 b),<sup>[5]</sup> and their application in a one-pot synthesis of the imidazo[1,5-*a*]pyridines **4**.<sup>[6]</sup> This new method toward imidazo[1,5-*a*]pyridines features a much broader scope, in that the presence of an AG and EWG in starting **1** is no longer required.

In continuation of our studies on application of diazo-compounds for the synthesis of nitrogen-containing heterocycles,<sup>[7]</sup> we investigated the reaction of pyridotriazoles with primary amides as a potential route to imidazo[1,5-*a*]pyridines. The 7-Cl-substituted triazole **1a**, which proved to be an effective carbene precursor,<sup>[1]</sup> was tested in the rhodium-catalyzed NH insertion reaction first (Table 1).<sup>[8]</sup> Indeed, the reaction of **1a** with BocNH<sub>2</sub> in the presence of a [Rh<sub>2</sub>(esp)<sub>2</sub>] catalyst at room temperature produced the corresponding picolyl amine **3aa** in 74% yield (entry 1).<sup>[9]</sup> Attempts to employ the 7-unsubstituted pyridotriazole **1b** under these reaction conditions failed. However, we were pleased to find that at 120 °C it underwent the insertion reaction to furnish the picolylamine **3ab** in 90% yield (entry 2).<sup>[10]</sup>

Next, we examined the scope of this NH insertion reaction. Thus, alkyl carbamates, such as *t*BuOCONH<sub>2</sub>, EtOCONH<sub>2</sub>, and BnOCONH<sub>2</sub> produced the picolyl amines **3ab–ad** in high yields (Table 1, entries 2–4). The reaction also worked efficiently with alkyl and aryl amides (entries 5–7), as well as with alkenyl amide (entry 8). Notably, a cyano group and alkenyl moiety, which normally react with metal carbenes, stayed intact under these reaction conditions (entries 6 and 8). Moreover, we found that phenyl urea and sulfonamide could also participate in this transformation to produce the insertion products **3ai** and **3aj** (entries 9 and 10). Secondary amides, such as oxazolidin-2-one (entry 11) and 3(2-*H*)-pyridazinone (entry 12), were also competent reaction partners. Notably, the reaction also efficiently proceeded with pyridotriazoles containing different substituents at the C3 position. Thus, 3-aryl pyridotriazoles (entries 13–16) and even 3-methyl pyridotriazole (entry 17) reacted smoothly to produce the desired NH insertion products. In addition, 4-methyl pyridotriazole (entry 18), *N*-fused quinolinotriazole (entry 19), and benzoxazolotriazole (entry 20) also under-



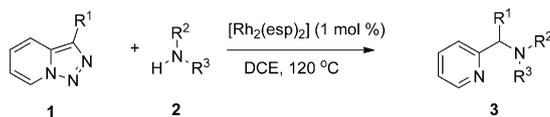
**Scheme 1.** Transannulation reactions of pyridotriazoles. DCE = 1,2-dichloroethane, esp =  $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid, Ts = 4-toluenesulfonyl.

[\*] Y. Shi, Dr. A. V. Gulevich, Prof. Dr. V. Gevorgyan  
Department of Chemistry, University of Illinois at Chicago  
845 W Taylor St., Room 4500, Chicago, IL 60607 (USA)  
E-mail: vlad@uic.edu  
Homepage: <http://www.chem.uic.edu/vggroup>

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**Table 1:** Substrate scope for the rhodium(II)-catalyzed reaction of pyridotriazoles with amides.<sup>[a,b]</sup>



Entry	1	3	Yield [%]	Entry	1	3	Yield [%]
1			74 <sup>[c]</sup>	11			66
2			90	12			75
3			91	13			89
4			65	14			75
5			85	15			81
6			87	16			77
7			76	17			88
8			85	18			66
9			75	19			63
10			68 <sup>[d]</sup>	20			91

[a] Reaction conditions: the triazole **1** (0.20 mmol), NH compounds **2** (1.5 equiv), and  $[\text{Rh}_2(\text{esp})_2]$  (1.0 mol %) were heated in 2 mL of anhydrous DCE at 120 °C until completion. [b] Yield of isolated product. [c] Performed at room temperature. [d] 3.0 mol %  $[\text{Rh}_2(\text{esp})_2]$ . Boc = *tert*-butoxycarbonyl.

went an efficient NH insertion reaction to afford the corresponding amides.

After developing the NH insertion reaction with various amides, we turned our attention to more challenging aromatic and aliphatic amines, which, as a result of their high basicity, may potentially deactivate the rhodium(II) catalyst. To our delight, reasonable to good yields in the reaction of **1b** with anilines were achieved upon raising the catalyst loading to 3 mol % (Table 2, entries 1–9). Thus, anilines bearing functional groups, such as halogens (entries 3 and 8),  $\text{CF}_3$  (entries 4 and 7), and  $\text{CO}_2\text{Me}$  (entry 5), efficiently underwent the reaction with **1b** to produce the insertion products. Moreover, sterically hindered 2,6-dichloro, and 2,6-diisopro-

pylaniline reacted smoothly to give the corresponding insertion products in reasonable yield (entries 8 and 9). In addition, an enamine also underwent the NH insertion reaction to form the corresponding product **3bj** (entry 10). Among aliphatic amines,  $\alpha\text{-CF}_3$ -substituted alkyl amines could undergo an NH insertion reaction, which was demonstrated by the reactions of **1b** with 2,2,2-trifluoro-1-phenylethane-1-amine (entry 11). Notably, the successful NH insertion reaction with  $\text{CF}_3$ -amino acid (entry 12) opens access to fluorinated opine derivatives (**3bl**).<sup>[11]</sup>

Along the lines of our studies on the development of new transformations toward heterocyclic molecules, we envisioned that the obtained picolylamides **3** could be cyclized

**Table 2:** Substrate scope for the rhodium(II)-catalyzed reaction of pyridotriazoles with anilines and aliphatic amines.<sup>[a,b]</sup>

Entry	Product	Yield [%]	Entry	Product	Yield [%]
1		88	7		71
2		63	8		90
3		80	9		47
4		86	10		91 <sup>[c]</sup>
5		72	11		87
6		76	12		82

[a] Reaction conditions: triazole **1** (0.20 mmol), NH compounds **2** (1.5 equiv), and  $[\text{Rh}_2(\text{esp})_2]$  (3.0 mol %) were heated in 2 mL of anhydrous DCE at 120 °C until completion. [b] Yield of isolated product. [c] 1.0 mol % of  $[\text{Rh}_2(\text{esp})_2]$ .

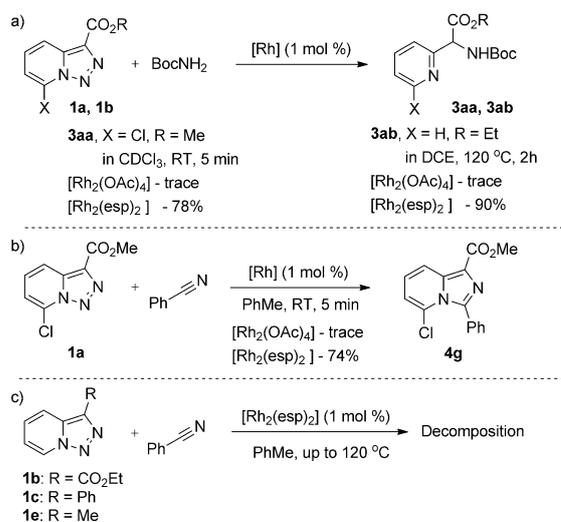
into the imidazopyridines **4** by a nucleophilic attack of the pyridine nitrogen atom at a suitably activated amide group (Table 3).<sup>[12]</sup> Accordingly, we developed a formal one-pot transannulation reaction of pyridotriazoles with primary amides which proceeds by the rhodium-catalyzed NH insertion reaction and subsequent cyclization into imidazo[1,5-a]pyridines (Table 3). Notably, this transannulation reaction of **1** with amides has a much broader scope compared to that of the previously developed transannulation reaction of **1** with nitriles (Scheme 1a). Thus, the AG is not necessary for the successful reaction, and the substituent at C3 is not limited to an electron-withdrawing group. Generally, the developed transannulation reaction allows an efficient synthesis of imidazo[1,5-a]pyridines containing aryl, alkenyl and alkyl substituents (Table 3, entries 1–6).

To understand the superior efficiency of the newly developed reaction of pyridotriazoles with amines over the previously reported reaction with nitriles, we performed reactions of the pyridotriazoles **1a,b** with  $\text{BocNH}_2$  and  $\text{PhCN}$  in the presence of different rhodium catalysts (Scheme 2). Thus, it was found that  $[\text{Rh}_2(\text{esp})_2]$ , indeed, is a superior catalyst over the previously used  $[\text{Rh}_2(\text{OAc})_4]$  for reactions of

**Table 3:** One-pot synthesis of imidazo[1,5-a]pyridines by NH insertion/cyclization process.<sup>[a,b]</sup>

Entry	<b>1</b>	<b>2</b>	<b>4</b>	Yield [%]
1				70
2				77
3				73
4				81
5				58
6				78

[a] Reaction conditions: triazole **1** (0.20 mmol), amides **2** (1.5 equiv), and  $[\text{Rh}_2(\text{esp})_2]$  (1.0 mol %) were heated in 2 mL of anhydrous DCE at 120 °C until completion. Then  $\text{TsOH}\cdot\text{H}_2\text{O}$  (1.0 equiv) and  $\text{Ac}_2\text{O}$  (0.2 mL) were added and the reaction mixture was heated at 120 °C. [b] Yield of isolated product.


**Scheme 2.** Reactions of pyridotriazoles with amides and nitriles.



- [13] For selected reviews on the rhodium-catalyzed NH insertion reactions of diazo compounds, see: a) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918–4931; b) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577–6605; c) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.
- [14] Analogously to pyridotriazole **1a**, phenyldiazoacetate quantitatively reacts with BocNH<sub>2</sub> in the presence of [Rh<sub>2</sub>(esp)<sub>2</sub>] catalyst at room temperature.
- [15] Test experiments indicated no NH insertion reaction of **1b** with BocNH<sub>2</sub> and PhNH<sub>2</sub> occurred under thermal conditions in the absence of a rhodium catalyst.
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## Communications

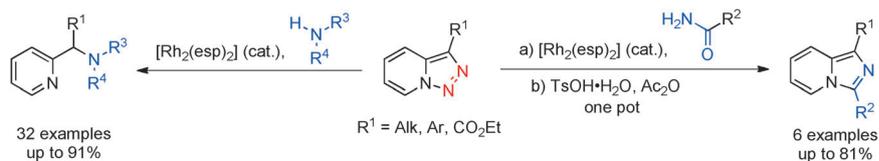


### Heterocycle Synthesis

Y. Shi, A. V. Gulevich,

V. Gevorgyan\*     

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