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Heterocycle Synthesis

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

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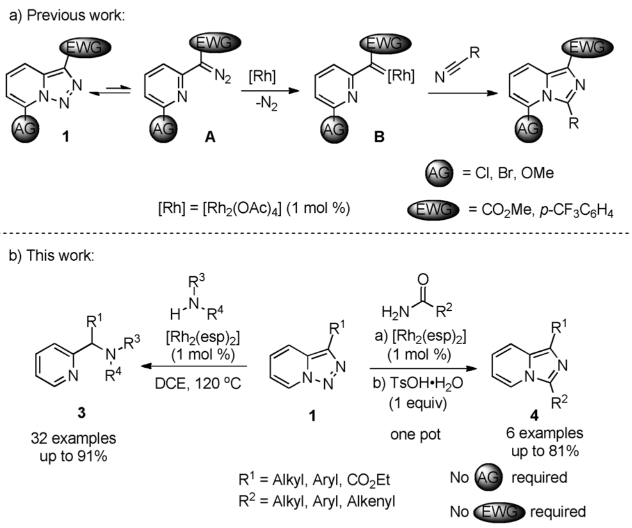
Abstract: *A general and efficient NH insertion reaction of rhodium pyridyl carbenes derived from pyridotriazoles was developed. Various NH-containing compounds, including amides, anilines, enamines, and aliphatic amines, smoothly underwent the NH insertion reaction to afford 2-picolylamine derivatives.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

Transition-metal-catalyzed denitrogenative transannulation of pyridotriazoles[1] is a powerful method for the synthesis of nitrogen-containing heterocycles.[2–4] 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 transannulation 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).[1a] 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),[5] and their application in a one-pot synthesis of the imidazo[1,5-a]pyridines **4**.[6] 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.



Scheme 1. Transannulation reactions of pyridotriazoles. DCE = 1,2-dichloroethane, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, Ts = 4-toluenesulfonyl.

In continuation of our studies on application of diazo-compounds for the synthesis of nitrogen-containing heterocycles,[7] 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,[1] was tested in the rhodium-catalyzed NH insertion reaction first (Table 1).[8] Indeed, the reaction of **1a** with $BocNH_2$ in the presence of a $[Rh_2(esp)_2]$ catalyst at room temperature produced the corresponding piclolyl amine **3aa** in 74 % yield (entry 1).[9] 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).[10]

Next, we examined the scope of this NH insertion reaction. Thus, alkyl carbamates, such as tBuOCONH$_2$, EtOCONH$_2$, and BnOCONH$_2$ 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 poisition. 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-

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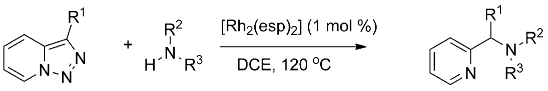
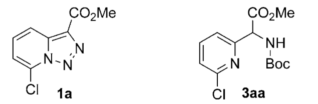
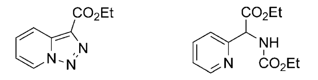
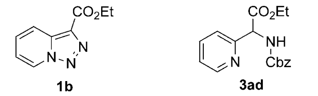
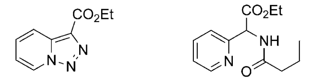
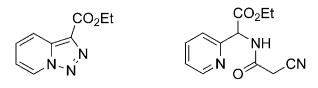
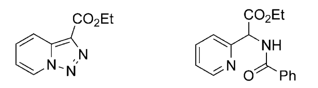
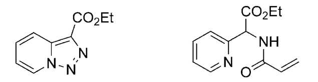
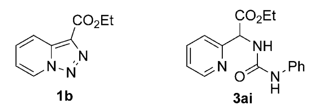
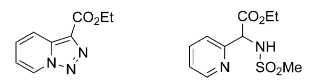
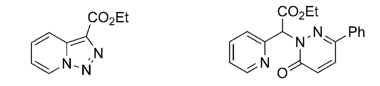
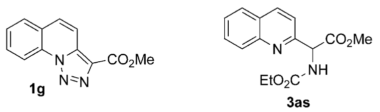
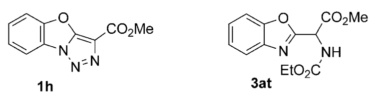
Table 1: Substrate scope for the rhodium(II)-catalyzed reaction of pyridotriazoles with amides.[a,b]



Entry	1	3	Yield [%]
1	 1a	3aa	74[c]
2	 1b	3ab	90
3	 1b	3ac	91
4	 1b	3ad	65
5	 1b	3ae	85
6	 1b	3af	87
7	 1b	3ag	76
8	 1b	3ah	85
9	 1b	3ai	75
10	 1b	3aj	68[d]
11	 1b	3ak	66
12	 1b	3al	75
13	 1c	3am	89
14	 1c	3an	75
15	 1c	3ao	81
16	 1d	3ap	77
17	 1e	3aq	88
18	 1f	3ar	66
19	 1g	3as	63
20	 1h	3at	91

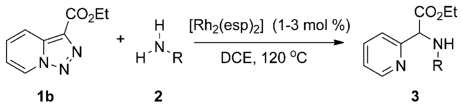
[a] Reaction conditions: the triazole **1** (0.20 mmol), NH compounds **2** (1.5 equiv), and $[Rh_2(esp)_2]$ (1.0 mol%) were heated in 2 mL of anhydrous DCE at 120°C until completion. [b] Yield of isolated product. [c] Performed at room temperature. [d] 3.0 mol% $[Rh_2(esp)_2]$. Boc = *tert*-butoxycarbonyl.

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), CF_3 (entries 4 and 7), and CO_2Me (entry 5), efficiently underwent the reaction with **1b** to produce the insertion products. Moreover, sterically hindered 2,6-dichloro, and 2,6-diisopropylaniline 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, α-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 CF_3-amino acid (entry 12) opens access to fluorinated opine derivatives (**3bl**).[11]

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

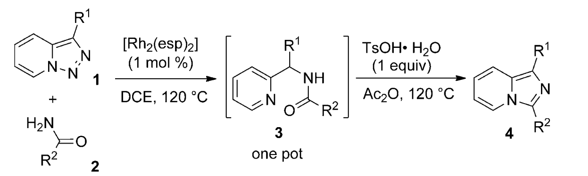
Table 2: Substrate scope for the rhodium(II)-catalyzed reaction of pyridotriazoles with anilines and aliphatic amines.[a,b]



Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	**3ba**	88	7	**3bg**	71
2	**3bb**	63	8	**3bh**	90
3	**3bc**	80	9	**3bi**	47
4	**3bd**	86	10	**3bj**	91[c]
5	**3be**	72	11	**3bk**	87
6	**3bf**	76	12	**3bl**	82

[a] Reaction conditions: triazole **1** (0.20 mmol), NH compounds **2** (1.5 equiv), and $[Rh_2(esp)_2]$ (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 $[Rh_2(esp)_2]$.

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

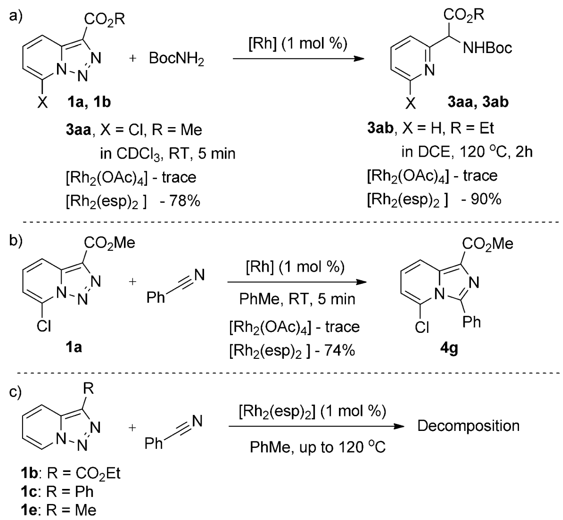


Entry	1	2	4	Yield [%]
1	**1b**	**2a**	**4a**	70
2	**1c**	**2b**	**4b**	77
3	**1e**	**2a**	**4c**	73
4	**1e**	**2b**	**4d**	81
5	**1b**	**2c**	**4e**	58
6	**1b**	**2d**	**4f**	78

[a] Reaction conditions: triazole **1** (0.20 mmol), amides **2** (1.5 equiv), and $[Rh_2(esp)_2]$ (1.0 mol%) were heated in 2 mL of anhydrous DCE at 120°C until completion. Then $TsOH{\cdot}H_2O$ (1.0 equiv) and Ac_2O (0.2 mL) were added and the reaction mixture was heated at 120°C. [b] Yield of isolated product.

into the imidazopyridines **4** by a nucleophilic attack of the pyridine nitrogen atom at a suitably activated amide group (Table 3).[12] 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 1 a). 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 $BocNH_2$ and PhCN in the presence of different rhodium catalysts (Scheme 2). Thus, it was found that $[Rh_2(esp)_2]$, indeed, is a superior catalyst over the previously used $[Rh_2(OAc)_4]$ for reactions of



Scheme 2. Reactions of pyridotriazoles with amides and nitriles.

pyridotriazole, both with amides and nitriles (Scheme 2a,b). It was also verified that amides showed higher reactivity towards rhodium(I)/pyridocarbene (i.e. **B**, Scheme 1) over nitriles, since even $[Rh_2(esp)_2]$ catalyst was not efficient for transannulation of unactivated pyridotriazoles **1b**,**c**,**e** with nitriles (Scheme 2c). It is believed that the NH insertion reaction of pyridotriazoles, analogously to that of phenyldiazoacetates, proceeds by an ylide mechanism.[13,14] However, it requires higher temperatures to produce sufficient amounts of a reactive diazo form (i.e. **B**, Scheme 1).[15] Overall, we believe that a superior efficiency of the newly developed reaction of pyridotriazoles with amines and amides over the previously reported reaction with nitriles is due to a combination of an increased potency of the rhodium catalyst and a higher reactivity of amines and amides over that of nitriles.

In conclusion, we have developed a general and efficient rhodium-catalyzed reaction of pyridotriazoles with amides and amines to produce valuable picolylamine derivatives. The subsequent cyclization provides expeditious access to various disubstituted imidazopyridines in a one-pot manner. The developed protocol allowed the synthesis of polysubstituted imidazopyridines, which were not accessible by previously reported transannulation reaction of pyridotriazoles with nitriles. Further studies on the unique reactivity of pyridotriazoles are currently underway in our lab.

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[8] For a 1,3-NH insertion reaction of iminocarbenes with nonbasic NH groups, see Ref. [4d].

[9] Other rhodium catalysts, such as $[Rh_2(OAc)_4]$ and $[Rh_2(Oct)_4]$, are also capable of catalyzing the reaction of the pyridotriazole **1a** with $BocNH_2$.

[10] The reaction of **1b** with $BocNH_2$ in the presence of other rhodium catalysts, such as $[Rh_2(OAc)_4]$ and $[Rh_2(Oct)_4]$, did not give any product.

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[14] Analogously to pyridotriazole **1a**, phenyldiazoacetate quantitatively reacts with $BocNH_2$ in the presence of $[Rh_2(esp)_2]$ catalyst at room temperature.

[15] Test experiments indicated no NH insertion reaction of **1b** with $BocNH_2$ and $PhNH_2$ occurred under thermal conditions in the absence of a rhodium catalyst.