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.

ransition-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 trans-



Scheme 1. Transannulation reactions of pyridotriazoles. DCE = 1,2dichloroethane, esp = α , α , α' , α' -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

nonnepage. http://www.chem.uic.edu/vggroup

[**] The support of the National Institutes of Health (GM 64444) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408335.

Angew. Chem. Int. Ed. 2014, 53, 1-6

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Wiley Online Library

These are not the final page numbers!

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 1a).^[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 1b),^[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.

In continuation of our studies on application of diazocompounds 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 rhodiumcatalyzed NH insertion reaction first (Table 1).^[8] Indeed, the reaction of **1a** with BocNH₂ in the presence of a [Rh₂(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 tBuOCONH₂, EtOCONH₂, and BnOCONH₂ 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, 4methyl pyridotriazole (entry 18), N-fused quinolinotriazole (entry 19), and benzoxazolotriazole (entry 20) also under-

Angewandte Communications

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

			$\mathbf{N}_{\mathbf{N}}^{\mathbf{R}^{1}}$ + $\mathbf{R}_{\mathbf{P}}^{\mathbf{R}^{2}}$ + $\mathbf{R}_{\mathbf{N}}^{\mathbf{R}^{3}}$	Rh ₂ (esp) ₂] (1 mol %)	\mathbf{R}^{1}		
		1	2		3		
Entry	1	3	Yield [%]	Entry	1	3	Yield [%]
1	CO_2Me N-N' Cl 1a	CO ₂ Me NH CI 3aa	74 ^[c]	11	N_{-N}	$ \begin{array}{c} $	66
2	N_{N}	CO ₂ Et NH N Boc 3ab	90	12	$ \begin{array}{c} CO_2Et \\ N_{-N}N \end{array} $ 1b	$ \begin{array}{c} CO_2Et \\ $	75
3	N = N = N	CO ₂ Et NH N CO ₂ Et 3ac	91	13	Ph N-N 1c	Ph NH N Boc 3am	89
4	CO ₂ Et	CO ₂ Et NH N Cbz 3ad	65	14	$ \begin{array}{c} $	Ph NH NH O Jan	75
5	$ \begin{array}{c} CO_2Et\\ N_N \\ N_N \end{array} $ 1b	CO ₂ Et NH 3ae	85	15	$ \begin{array}{c} $	Ph NH 3ao	81
6	N_{N}	$ \begin{array}{c} CO_2Et \\ N \\ O \\ CN \\ 3af \end{array} $	87	16	$p - C_6 H_4 OMe$ $N - N^N$ 1d	p-C ₆ H ₄ OMe NH Boc 3ap	77
7	N_{N}	$ \begin{array}{c} \text{CO}_2\text{Et} \\ \text{NH} \\ \text{NOPh} \\ \text{3ag} \end{array} $	76	17		Me NH N Boc 3aq	88
8	$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\$	CO ₂ Et NH NO 3ah	85	18	$ \begin{array}{c} Me & CO_2Me \\ & & \\ & $	Me CO ₂ Me NH N Boc 3ar	66
9	$ \begin{array}{c} $	CO ₂ Et NH NH NH NH NH NH	75	19	NN-CO ₂ Me	EIO ₂ CO ₂ Me	63
10	$N_{N}^{O_2Et}$	CO ₂ Et NH N SO ₂ Me 3aj	68 ^[d]	20	$ \begin{array}{c} $	CO ₂ Me N NH EtO ₂ C	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), CF₃ (entries 4 and 7), and CO₂Me (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, α -CF₃-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 CF₃-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

www.angewandte.org

2

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

Table 2:	Substrate se	cope for t	the rho	dium(I	I)-catalyzed	reaction of
pyridotri	azoles with	anilines a	and alip	hatic a	amines. ^[a,b]	

	CO ₂ E	t <u> </u>	1 ₂ (esp) ₂] (1-3 i	mol %)	
		H ^N R	DCE, 120 °C		
	1b	2		3	
Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	3ba	88	7	3bg CF ₃	71
2	CO ₂ Et	63	8	EtO ₂ C ^{CI} N N 3bh	90
3		80	9	EtO ₂ C ^{/Pr}	47
	3bc F CO ₂ Et			CO ₂ Et	
4	3bd CF ₃	86	10	3bj O	91 ^[c]
5	NH 3be CO ₂ Me	72	11	EtO ₂ C CF ₃ N Ph N 3bk	87
6	CO ₂ Et NH 3bf	76	12	EtO ₂ C CF ₃ N CO ₂ Et	82



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 BocNH₂ 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

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



[a] Reaction conditions: triazole 1 (0.20 mmol), amides 2 (1.5 equiv), and [Rh₂(esp)₂] (1.0 mol%) were heated in 2 mL of anhydrous DCE at 120°C until completion. Then TsOH·H₂O (1.0 equiv) and Ac₂O (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.

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

www.angewandte.org

Angewandte Communications

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 [Rh2(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.

Received: August 18, 2014 Revised: September 23, 2014 Published online:

Keywords: annulations · carbenes · heterocycles · rhodium · synthetic methods

- a) S. Chuprakov, F. Hwang, V. Gevorgyan, Angew. Chem. Int. Ed. 2007, 46, 4757-4759; Angew. Chem. 2007, 119, 4841-4843;
 b) S. Chuprakov, V. Gevorgyan, Org. Lett. 2007, 9, 4463-4466. For review, see: c) B. Chattopadhyay, V. Gevorgyan, Angew. Chem. Int. Ed. 2012, 51, 862-872; Angew. Chem. 2012, 124, 886-896.
- [2] For reviews on reactions of metallocarbenes derived from N-sulfonyl 1,2,3-triazoles, see: a) H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* 2014, 43, 5151-5162; b) A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* 2013, 52, 1371-1373; *Angew. Chem.* 2013, 125, 1411-1413.
- [3] For transannulation reactions of N-sulfonyl triazoles, see: a) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, J. Am. Chem. Soc. 2008, 130, 14972-14974; b) T. Miura, M. Yamauchi, M. Murakami, Chem. Commun. 2009, 1470-1471; c) B. Chattopadhyay, V. Gevorgyan, Org. Lett. 2011, 13, 3746-3749; d) B. T. Parr, S. A. Green, H. M. L. Davies, J. Am. Chem. Soc. 2013, 135, 4716-4718; e) J. E. Spangler, H. M. L. Davies, J. Am. Chem. Soc. 2013, 135, 6802-6805; f) J. S. Alford, J. E. Spangler, H. M. L. Davies, J. Am. Chem. Soc. 2013, 135, 11712-11715; g) B. T. Parr, H. M. L. Davies, Angew. Chem. Int. Ed. 2013, 52, 10044-10047; Angew. Chem. 2013, 125, 10228-10231; h) M. Zibinsky, V. V. Fokin, Angew. Chem. Int. Ed. 2013, 52, 1507-1510; Angew. Chem. 2013, 125, 1547-1550; i) S. Chuprakov, S. W. Kwok, V. V. Fokin, J. Am. Chem. Soc. 2013, 135, 4652-4655; j) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart, M. Murakami, J. Am. Chem. Soc. 2013, 135, 13652-13655; k) T. Miura, K. Hiraga, T. Biyajima, T. Nakamuro, M. Murakami, Org.

Lett. 2013, 15, 3298-3301; l) E. E. Schultz, R. Sarpong, J. Am. Chem. Soc. 2013, 135, 4696-4699; m) Y. Shi, V. Gevorgyan, Org. Lett. 2013, 15, 5394-5396; n) T. Miura, Y. Funakoshi, M. Murakami, J. Am. Chem. Soc. 2014, 136, 2272-2275; o) C. Kim, S. Park, D. Eom, B. Seo, P. H. Lee, Org. Lett. 2014, 16, 1900-1903; p) J. Yang, C. Zhu, X. Tang, M. Shi, Angew. Chem. Int. Ed. 2014, 53, 5142-5146; Angew. Chem. 2014, 126, 5242-5246; q) H. Shang, Y. Wang, Y. Tian, J. Feng, Y. Tang, Angew. Chem. Int. Ed. 2014, 53, 5662-5666; Angew. Chem. 2014, 126, 5768-5772; r) K. Chen, Z.-Z. Zhu, Y.-S. Zhang, X.-Y. Tang, M. Shi, Angew. Chem. Int. Ed. 2014, 53, 6645-6649; Angew. Chem. 2014, 126, 6763-6767; s) B. Rajagopal, C.-H. Chou, C.-C. Chung, P.-C. Lin, Org. Lett. 2014, 16, 3752-3755; t) R.-Q. Ran, J. He, S.-D. Xiu, K.-B. Wang, C.-Y. Li, Org. Lett. 2014, 16, 3704-3707; u) F. Medina, C. Besnard, J. Lacour, Org. Lett. 2014, 16, 3232-3235.

- [4] For other reactions of N-sulfonyl triazoles, see: a) N. Grimster, L. Zhang, V. V. Fokin, J. Am. Chem. Soc. 2010, 132, 2510-2511; b) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher, V. V. Fokin, J. Am. Chem. Soc. 2009, 131, 18034-18035; c) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, J. Am. Chem. Soc. 2012, 134, 14670-14673; d) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit, V. V. Fokin, J. Am. Chem. Soc. 2014, 136, 195-202; e) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, J. Am. Chem. Soc. 2011, 133, 10352-10355; f) J. S. Alford, H. M. L. Davies, Org. Lett. 2012, 14, 6020-6023; g) T. Miura, T. Biyajima, T. Fujii, M. Murakami, J. Am. Chem. Soc. 2012, 134, 194-196; h) T. Miura, T. Tanaka, T. Biyajima, A. Yada, M. Murakami, Angew. Chem. Int. Ed. 2013, 52, 3883-3886; Angew. Chem. 2013, 125, 3975-3978; i) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima, M. Murakami, J. Am. Chem. Soc. 2012, 134, 17440-17443; j) N. Selander, B. T. Worrell, V. V. Fokin, Angew. Chem. Int. Ed. 2012, 51, 13054-13057; Angew. Chem. 2012, 124, 13231-13234; k) A. Boyer, Org. Lett. 2014, 16, 1660-1663; l) D. J. Jung, H. J. Jeon, J. H. Kim, Y. Kim, S. Lee, Org. Lett. 2014, 16, 2208-2211; m) D. Yadagiri, P. Anbarasan, Org. Lett. 2014, 16, 2510-2513; n) T. Miura, Y. Funakoshi, T. Tanaka, M. Murakami, Org. Lett. 2014, 16, 2760-2763; o) T. Miura, T. Nakamuro, K. Hiraga, M. Murakami, Chem. Commun. 2014, 50, 10474 - 10477.
- [5] For report on 2-pycolylamine-containing bioactive molecules, see: a) K. Tsuboi, D. A. Bachovchin, A. E. Speers, T. P. Spicer, V. Fernandez-Vega, P. Hodder, H. Rosen, B. F. Cravatt, J. Am. Chem. Soc. 2011, 133, 16605-16616.
- [6] For biologically active imidazopyridines, see: M. Reutlinger, T. Rodrigues, P. Schneider, G. Schneider, Angew. Chem. Int. Ed. 2014, 53, 582-585; Angew. Chem. 2014, 126, 593-596, and references therein.
- [7] a) A. V. Gulevich, V. Helan, D. J. Wink, V. Gevorgyan, Org. Lett. **2013**, 15, 956–959; b) A. Kuznetsov, A. V. Gulevich, D. J. Wink,
 V. Gevorgyan, Angew. Chem. Int. Ed. **2014**, 53, 9021–9025;
 Angew. Chem. **2014**, 126, 9167–9171.
- [8] For a 1,3-NH insertion reaction of iminocarbenes with nonbasic NH groups, see Ref. [4d].
- [9] Other rhodium catalysts, such as [Rh₂(OAc)₄] and [Rh₂(Oct)₄], are also capable of catalyzing the reaction of the pyridotriazole 1a with BocNH₂.
- [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.
- [11] For selected reports on bioactive iminodicarboxylic acids and opines, see: a) L. W. Moore, W. S. Chilton, M. L. Canfield, *Appl. Environ. Microbiol.* **1997**, *63*, 201–207; b) W. S. Chilton, A. Petit, M.-D. Chilton, Y. Dessaux, *Phytochemistry* **2001**, *58*, 137–142.
- [12] Y. P. Kovtun, Y. A. Prostota, Chem. Heterocycl. Compd. 2000, 36, 557-559.

www.angewandte.org

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2014, 53, 1-6

These are not the final page numbers!



- [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 BocNH₂ in the presence of $[Rh_2(esp)_2]$ catalyst at room temperature.
- [15] Test experiments indicated no NH insertion reaction of 1b with BocNH₂ and PhNH₂ occurred under thermal conditions in the absence of a rhodium catalyst.



Communications

Heterocycle Synthesis

Y. Shi, A. V. Gulevich, V. Gevorgyan*

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



Insert here: 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. esp = $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid, Ts = 4-toluenesulfonyl.

6 www.angewandte.org

C 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!