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# COMMUNICATION

## Palladium-Catalyzed Denitrogenative Functionalizations of Benzotriazoles with Alkenes and 1,3-Dienes

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Pd-catalyzed denitrogenative functionalizations of benzotriazoles with alkenes and 1,3-dienes are developed, which enable the rapid access of diverse *ortho*-amino styrenes and 2-vinylindolines, respectively. This study shows the great potential of benzotriazoles as a [1C]-synthon in cross-coupling reaction and an aza-[3C] synthon in cycloaddition reaction.

Since their discovery in the 1860s,<sup>1</sup> arenediazonium salts have evolved into a class of reactive electrophiles displaying versatile reactivity from free-radical chemistry to organometallic synthesis.<sup>2</sup> Generally, arenediazonium salts are prepared from the corresponding anilines through diazotization. However, the high nucleofugic property of diazonium function makes these compounds unstable and potentially explosive, and thus have to be used immediately after preparation. To address this issue, considerable effort has been devoted to developing new methods to access stabilized arenediazonium salts.<sup>3</sup> In addition, some operationally simple protocols to effect the generation of arenediazonium salts and following transformations in one pot have also been developed.<sup>4</sup> Despite such advances, these methods usually necessitate the usage of expensive reagents or/and take additional synthetic operations, which to some extent compromises their applicability. Thus, the development of conceptually novel and synthetically useful method to access arenediazonium salts is highly desirable.

Benzotriazoles represent an important class of heterocycles that are recognized for their versatile reactivities.<sup>5</sup> In particular, benzotriazoles bearing a strong electron-

withdrawing group on

A) Denitrogenative [3+2] cycloaddition of benzotriazoles with alkynes (Nakamura's work)





C) Denitrogenative alkenylation benzotriazoles with alkenes and 1,3-dienes (this work



**Scheme 1** Application of benzotriazoles as synthetic equivalent of orthoamino arenediazoniums.

N1 position could undergo ring opening to form its isomeric ortho-amino-arenediazonium species via a Dimroth-type equilibrium.<sup>6</sup> In this context, benzotriazoles could be viewed as a masked ortho-amino-arenediazonium. While such potential seems to be attractive, it has been rarely explored by synthetic community during the past decades. In 2009, Nakamura and reported co-workers а novel palladium-catalyzed cycloaddition of Ndenitrogenative formal [3+2] aroylbenzotriazoles with internal alkynes (Scheme 1A). Mechanistically, the reaction was assumed to proceed via an ortho-amino-arenediazonium intermediate in situ generated from the benzotriazole precursor. This discovery open a new avenue to utilize benzotriazole as a synthetic equivalent of ortho-amino-arenediazonium in transition-metal-catalyzed reactions. However, the harsh conditions and moderate efficiency of the transformation restrict its widespread application in organic synthesis. Thus, the development of a general, efficient and robust method to effect the ring open of

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benzotriazoles followed by synthetically useful transformations is of great importance.<sup>8</sup>

Recently, we reported the unprecedented Pd-catalyzed denitrogenative Suzuki coupling and Suzuki carbonylative reactions of benzotriazoles with boronic acids (Scheme 1B).<sup>9</sup> Key to the success relies on a rationally designed strategy to effect the ring opening of benzotriazoles, which enables in situ generation of arenediazonium tetrafluoroborate species under mild conditions. Encouraged by this discovery, we envisioned that it was feasible to integrate the ring-opening chemistry of benzotriazole with other synthetically useful transformations. As continuation of our interest on this topic, we report herein the novel Pd-catalyzed denitrogenative functionalizations of benzotriazoles with alkenes and 1,3-dienes, which enables the rapid access of diverse ortho-amino styrenes and 2-vinylindolines, respectively (Scheme 1C).

Table 1 Condition optimization<sup>*a,b*</sup>

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	N N Tf 1a	+ $Ph$ $2a$ $Catalyst (5%)  PPh_3 (30%)  AgBF_4 (250%)  other conditions$	NHTf 3a
entry	Pd-catalyst	other conditions	yield of <b>3a</b>
1	Pd(OAc) <sub>2</sub>	toluene, 80 °C	n.r.
2	PdCl <sub>2</sub>	toluene, 80 °C	n.r.
3	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	toluene, 80 °C	n.r.
4	$Pd(CF_3CO_2)_2$	toluene, 80 °C	24%
5	Pd(PPh₃)₁	toluene, 80 °C	38%
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CH₃CN, 80 °C	81%
7	Pd(PPh₃)₄	CH₃CN, 90 °C	86%
8	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CH <sub>3</sub> CN, 100 °C	78%
9 <sup>c</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CH₃CN, 100 °C	43%

<sup>*a*</sup> Reaction conditions: **1a** (0.30 mmol), **2a** (0.90 mmol), Pd-cat (0.015 mmol), PPh<sub>3</sub> (0.09 mmol) and AgBF<sub>4</sub> (0.75 mmol) in solvent (3.0 mL). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> No PPh<sub>3</sub> was used. n.r. = no reaction. Tf = trifluoromethanesulfonyl.

We began our study by conducting the reaction of benzotriazole (1a) and styrene (2a) under the previously employed catalyst system [Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, AgBF<sub>4</sub>, toluene, 80 °Cl.<sup>9</sup> To our disappointment, the expected denitrogenative alkenylation product was not detected (Table 1, entry 1). Fortunately, a rapid survey of palladium sources revealed that while PdCl<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> failed to give promising results (entries 2 and 3), Pd(CF<sub>3</sub>CO<sub>2</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> exhibited superior reactivity by providing 3a in 24% and 38% yields, respectively (entries 4 and 5). Encouraged by these results, we further screened other reaction parameters using Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst. Pleasingly, we found that replacing toluene with MeCN could significantly improve the yield to 81% (Entry 6). Furthermore, increasing the reaction temperature to 90 °C also exerted a beneficial effect, thus delivering 3a in 86% yield (Entry 7). A slightly lower yield was obtained when the reaction was conducted at 100 °C (Entry 8). Of note, the yield decreased significantly in the absence of PPh<sub>3</sub> (Entry 9).

With the optimized conditions in hand, we turned to examine the scope and limitation of the reaction (Table 2). As shown, a variety of benzotriazoles bearing different substitutents at the aryl moiety provided the corresponding products in good to excellent yields (up to 96%), regardless of the electronic nature or substitution patterns (**3a-j**). Among them, the structure of **3f** was identified by the X-ray

 Table 2 Scope of denitrogenative alkenylation<sup>a,b</sup>



<sup>&</sup>lt;sup>*a*</sup> Reaction conditions: **1** (0.30 mmol), **2** (0.90 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.015 mmol), PPh<sub>3</sub> (0.09 mmol) and AgBF<sub>4</sub> (0.75 mmol) in MeCN (3.0 mL). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> **2u** (0.45 mmol). <sup>*d*</sup> **2w** (1.8 mmol). <sup>*e*</sup> The reaction was conducted with ethylene balloon (1 atm).

crystallographic study.<sup>10</sup> Of note, the reaction proceeded for the sterically hindered ortho-methyl smoothly benzotriazole, which gave the corresponding product (3j) with comparable efficiency. In addition, replacing the phenyl ring of benzotriazoles with naphthalene backbone did not hamper the reaction. Besides the benzotriazoles, a broad range of alkenes were also examined in the reactions. Pleasingly, diverse styrene derivatives were proved to be suitable substrates by delivering the alkenylation adducts (3I-s) in good to excellent yields, irrespective of the electronic nature and substitution patterns of the aryl moiety. 2-vinylnaphthalenethe, 3-vinylindole and 3-vinylpyridine were also amenable for the reaction (3t-v). Importantly, ethyl acrylate and ethylene were also tolerated well, affording 3w and 3x in 92% and 88% yields, respectively. However, the aliphatic alkene and internal alkene failed to give the desired products (3y and 3z).

Out of our expectation, when 1-phenyl-1,3-diene (**3a**) was employed in the reaction, the corresponding denitrogenative alkenylation product was not detected. Instead, 2-vinylindolin **5a**, a formal denitrogenative [3+2] cycloadduct, was identified predominantly. Notably, Indolines represent an important class of structural motifs widely distributed in bioactive natural products and pharmaceuticals.<sup>11</sup> In this context, the above Published on 10 October 2017. Downloaded by Freie Universitaet Berlin on 10/10/2017 12:58:35

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reaction may provide a new method to access this type of of scaffold.<sup>12</sup> To test the viability of this method, we evaluated a

### Table 3 Scope of Denitrogenative [3+2] Cycloaddition<sup>a,b</sup>



<sup>o</sup> Reaction conditions: **1** (0.30 mmol), **4** (0.60 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.015 mmol), PPh<sub>3</sub> (0.09 mmol) and AgBF<sub>4</sub> (0.75 mmol) in MeCN (3.0 mL). <sup>b</sup> Isolated yield.

range of benzotriazoles using **4a** as reaction partner (Table 3). Pleasingly, all of the substrates bearing electron-withdrawing, neutral, and -donating substituents on the aromatic ring tolerated well in the reactions, and thus the corresponding products (**5a-i**) were obtained in good to excellent yields. Furthermore, an array of 1-aryl 1,3-dienes bearing different substituents were also evaluated with **1a** as reaction partner. Gratifyingly, all of the reactions proceeded smoothly to yield the corresponding products (**5j-t**), which further illustrates the generality of our method.



Scheme 2 Mechanistic rationalization.

Based on our previous studies as well as some inspiring cases,  $^{9,13}$  the plausible mechanisms of above transformations

are rationalized in Scheme 2. Thus, benzotriazoles (1) could advance to the arenediazonium tetrafluoroborates **A** through a Dimroth-type equilibrium with the action of a synergistic activating-stabilizing effect. The resulting arenediazonium species would then undergo oxidative addition with Pd(0)catalyst to generate the Pd(II)-complex **B**, from which, two pathways, namely  $\beta$ -hydride elimination and nucleophilic attack, are possible. The former one leads to Heck-type reaction product **3** via intermediate **C**, while the latter one provides formal [3+2] cycloaddition product **5**.

To investigate the origin of distinct chemoselectivity between 1,3-dienes and simple alkenes, DFT calculation was carried out.<sup>14</sup> Shown in Fig. 1a, the computation confirms that, after alkene insertion, the activation energy of  $\theta$ -hydride elimination is significantly lower than that of formal [3+2] cyclization for the simple alkene substrates; and vice versa for 1,3-dienes. This difference could be attributed to two factors. Firstly, the highly electrophilic nature of  $\pi$ -allyl-palladium species in the 1,3-diene version of intermediate **B**, comparing to that of simple alkenes, makes it much less facile to undergo  $\beta$ -H elimination.<sup>13c</sup> Instead, it would ultimately undergo an intramolecular N-allylation to give formal [3+2] cycloadducts 5.<sup>13d-f</sup> Secondly, there exists a significant agnostic effect for the intermediate B generated using substrate 2. The C-H bond ciscoplanar with the C-Pd bond is significantly lengthened comparing to the other benzylic C-H bond (Fig. 1b). The Laplacian bond order of the cis-coplanar C-H bond is only 0.64, which also shows the agnostic effect, comparing to a value of 0.8~0.9 for average C-H bonds.<sup>15</sup> This effect, which is almost absent in the cases using 1,3-diene substrates, significantly lowers the energy required for  $\beta$ -hydride elimination pathway.



**Fig. 1** (a) Calculated activation Gibbs free energy of  $\beta$ -hydride elimination and formal [3+2] cyclization after the formation of intermediate **B**. (b) Optimized structure and geometry parameters of intermediate **B** for substrate **2a**.<sup>14</sup>.

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In summary, the palladium-catalyzed denitrogenative functionalizations of benzotriazoles with alkenes and 1,3dienes are reported. Mechanistically, both transformations proceed through an ortho-amino arenediazonium salt in situ generated from the ring opening of benzotriazole. Differently, the reactions with simple alkenes follows a mechanism of Heck-type coupling and the reactions with 1,3-dienes adopts a formal [3+2] mechanism. DFT calculation was conducted to explain the distinct behavior of simple alkenes and 1,3-dienes in these transformations. The present study not only further showcases the appealing synthetic utility of benzotriazoles as a [1C] synthon in cross-coupling reactions, but also extends its application as an aza-[3C] synthon in cycloaddition reactions. We anticipate that more synthetically useful transformations will be developed under the guidance of this concept, and relevant work is currently underway in our laboratory.

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### **Conflicts of interest**

There are no conflicts to declare.

### Notes and references

- 1 P. Griess, Justus Liebigs Ann. Chem., 1858, 106, 123.
- 2 (a) C. Galli, *Chem. Rev.*, 1988, **88**, 765; (b) A. Roglands, A. Pla-Quintana and M. Moreno-Manas, *Chem. Rev.*, 2006, **106**, 4622; (c) H. Bonin, E. Fouquet and F. X. Felpin, *Adv. Synth. Catal.*, 2011, **353**, 3063; (d) D. P. Hari and B. König, *Angew. Chem. Int. Ed.*, 2013, **52**, 4734; (e) N. Oger, M. d'Halluin, E. L. Grognec and F. X. Felpin, *Org. Process Res. Dev.*, 2014, **18**, 1786.
- For examples, see: (a) D. T. Flood, Org. Synth., 1943, 2, 295;
  (b) M. P. Doyle and W. J. Bryker, J. Org. Chem., 1979, 44, 1572;
  (c) V. D. Filimonov, M. Trusova, P. Postnikov, E. A. Krasnokutskaya, Y. M. Lee, H. Y. Hwang, H. Kim and K. W. Chi, Org. Lett., 2008, 10, 3961;
  (d) M. Barbero, M. Crisma, I. Degani, R. Fochi and P. Perracino, Synthesis, 1998, 1171;
  (e) J. R. Peterson and T. J. Mitchison, Chem. Biol., 2002, 9, 1275.
- For examples, see: (a) M. B. Andrus and C. Song, Org. Lett., 2001, 3, 3761; (b) B. Schmidt, R. Berger and F. Holter, Org. Biomol. Chem., 2010, 8, 1406; (c) T. Saeki, E. C. Son and K. Tamao, Org. Lett., 2004, 6, 617; (d) C. Y. Liu, A. Gavryushin and P. Knochel, Chem Asian J., 2007, 2, 1020; (e) F. Mo, D. Qiu, Y. Jiang, Y. Zhang and J. Wang, Tetrahedron Lett., 2011, 52, 518.
- 5 For reviews, see: (a) A. R. Katritzky and S. Rachwal, *Chem. Rev.*, 2010, **110**, 1564; (b) A. R. Katritzky and S. Rachwal, *Chem. Rev.*, 2011, **111**, 7063; (c) A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
- 6 (a) C. L. Habraken, C. Erkelens, J. R. Mellema and P. Cohen-Fernandes, J. Org. Chem., 1984, 49, 2197; (b) A. R. Katritzky, F. B. Ji, W. Q. Fan, J. K. Gallos, J. V. Greenhill and R. W. King, J. Org. Chem., 1992, 57, 190; (c) X. A. Àlvarez Micó, T. Ziegler and L. R. Subramanian, Angew. Chem. Int. Ed., 2004, 43, 1400; (d) A. R. Katritzky, R. Akue-Gedu and A. V. Vakulenko, ARKIVOC, 2007, 5; (e) A. R. Katritzky, L. Khelashvili, K. N. B. Le, P. P. Mohapatra and P. J. Steel, J. Org. Chem., 2007, 72,

5805; (f) M. Uhde, M. U. Anwar and T. Ziegler, *Synth. Commun.*, 2008, **38**, 881.

- 7 I. Nakamura, T. Nemoto, N. Shiraiwa and M. Terada, *Org. Lett.*, 2009, **11**, 1055.
- 8 For the recent advance on this subject, see: (a) M. Teders, A. Gómez-Suárez, L. Pitzer, M. N. Hopkinson and F. Glorius. *Angew. Chem. Int. Ed.*, 2017, **56**, 902; (b) M. Teders, L. Pitzer, S. Buss, F. Glorius, *ACS Catal.*, 2017, **7**, 4053.
- 9 Y. H. Wang, Y. F. Wu, Y. H. Li and Y. F. Tang, *Chem. Sci.*, 2017, **8**, 3852.
- 10 X-ray CCDC 1564272 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.
- 11 For reviews, see: (a) D. Crich and A. Banerjee, Acc. Chem. Res., 2007, 40, 151; (b) D. Zhang, H. Song and Y. Qin, Acc. Chem. Res., 2011, 44, 447; (c) P. Siengalewicz, T. Gaich and J. Mulzer, Angew. Chem., Int. Ed., 2008, 47, 8170; (d) D. L. Boger, C. W. Boyce, R. M. Garbaccio and J. A. Goldberg, Chem. Rev., 1997, 97, 787; For selected examples, see: (e) S. Adachi, K. Koike and I. Takayanagi, Pharmacology, 1996, 53, 250; (f) N. S. Williams, A. W. G. Burgett, A. S. Atkins, X. Wang, P. G Harran and S. L. McKnight, Proc. Natl. Acad. Sci. U. S. A., 2007, 104, 2074; (g) H. Zhao, X. He, A. Thurkauf, D. Hoffman, A. Kieltyka, R. Brodbeck, R. Primus and W. F. Wasley, Bioorg. Med. Chem. Lett., 2002, 12, 3111; (h) S. Samwel, J. O. Odalo, M. H. H. Nkunya, C. C. Joseph and Koorbanally, N. A. Phytochemistry, 2011, 72, 1826.
- 12 For examples, see: (a) R. Amrani, A. Thomas, E. Brenner, R. Schneider and Y. Fort, *Org. Lett.*, 2003, 5, 2311; (b) H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.* 2005, 70, 5164; (c) T. Noji, H. Fujiwara, K. Okano and H. Tokuyama, *Org. Lett.*, 2013, 15, 1946; (d) R. Miyaji, K. Asano and S. Matsubara, *Org. Lett.*, 2013, 15, 3658; (e) T. Touge and T. Arai, *J. Am. Chem. Soc.*, 2016, 138, 11299; (f) Y. He, C. Zhang, M. Fan, Z. Wu and D. Ma, *Org. Lett.*, 2015, 17, 496.
- (a) J. M. O'Connor, B. J. Stallman, W. G. Clark, A. Y. L. Shu, R. E. Spada, T. M. Stevenson and H. A. Dieck, J. Org. Chem., 1983, 48, 807; (b) R. C. Larock, N. Berrios-Pefia and K. Narayanan, J. Org. Chem., 1990, 55, 3447; (c) G. L. J. Bar, G. C. Lloyd-Jones and K. I. Booker-Milburn, J. Am. Soc. Chem., 2005, 127, 7308; (d) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones and K. I. Booker-Milburn, J. Am. Soc. Chem., 2008, 130, 10066; (e) S. S. Chen, J. Meng, Y. H. Li and Z. Y. Han, J. Org. Chem., 2016, 81, 9402; (f) S. S. Chen, M. S. Wu and Z. Y. Han, Angew. Chem. Int. Ed., 2017, 56, 6641.
- 14 Computations are carried out at RI-DSD-PBEP86-D3/def2-TZVP//M06/[LANL2TZ(f)+def2-SV(P)] level (LANL2TZ(f) for Pd and Ag atoms) with the Gaussian 09 and ORCA 4.0.1 program. For references of the programs, see: (a) M. Frisch, J. Trucks, H. Schlegel, et al. Gaussian 09, Revision D.01, *Gaussian, Inc.*, Wallingford CT, 2013 (for the full list of authors, see Supporting Information); (b) F. Neese, WIREs Comput. Mol. Sci., 2012, 2, 73; For references of the computation level, see: (c) S. Kozuch and J. M. L. Martin, J. Comput. Chem., 2013, 34, 2327; (d) F. Weigend and R. Ahlrichs, Phys. Chem. Chem. Phys., 2005, 7, 3297; (e) Y. Zhao and D. Truhlar, Theor. Chem. Acc., 2008, 120, 215; (f) L. E. Roy and P. J. Hay, R. L. Martin, J. Chem. Theory Comput., 2008, 4, 1029.
- 15 The Laplacian bond order was calculated using Multiwfn 3.4.1 program (dev. version). For the references, see: (a) T. Lu and F. Chen, *J. Comput. Chem.*, 2012, **33**, 580; (b) T. Lu, F. Chen, *J. Phys. Chem.* A, 2013, **117**, 3100.

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