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Palladium(II)-Catalyzed Enantioselective Azidation of Unactivated Alkenes **

Xiaonan Li, [a] Xiaoxu Qi,[a] Chuanqi Hou,[a] Pinhong Chen,*[a] and Guosheng Liu*[a,b]

In memory of Professor Kilian Muñiz

Abstract: The first Pd-catalyzed enantioselective azidation of unactivated alkenes has been established by using readily accessible 1-azido-1,2-benziodoxol-3(1H)-one (ABX) as an azidating reagent, which affords a wide variety of structurally diverse 3-N_3-substituted piperidines in good yields with excellent enantioselectivities. The reaction features good functional group compatibility and mild reaction conditions. Notably, both an electrophilic azidating reagent and the sterically bulky chiral pyridinyl-oxazoline (Pyox) ligand are crucial to the successful reaction.

Optically pure 3-aminopiperidines widely exist in natural alkaloids[1] (e.g., slaframine)[2] and drugs (e.g., ibrutinib, nemonoxacin and linagliptin)[3] as shown in Figure 1, which have been extensively applied to treat B cell cancers, inhibit DNA gyrase, control blood sugar and so on. Therefore, the exploration of efficient methods for their synthesis has received much attention over the last several decades in organic synthesis, while a *multi*-step process is often required.[4] So far, an efficient tool for their asymmetric synthesis still remains elusive.[5] Owing to the diverse transformations of organic azides, [6] 3-aminopiperidines can be easily prepared from the corresponding 3-azidopiperidines via a reduction process (Figure 1). In this regard, asymmetric azidation reaction represents an interesting approach for their synthesis. Thus, the development of the asymmetric azidation is highly demand.

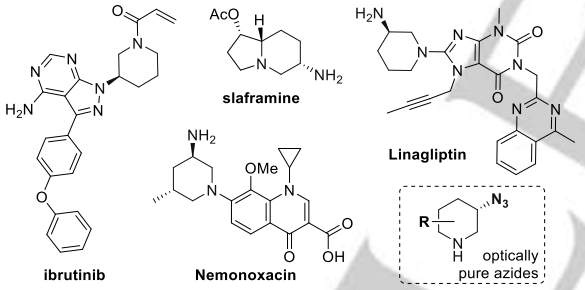
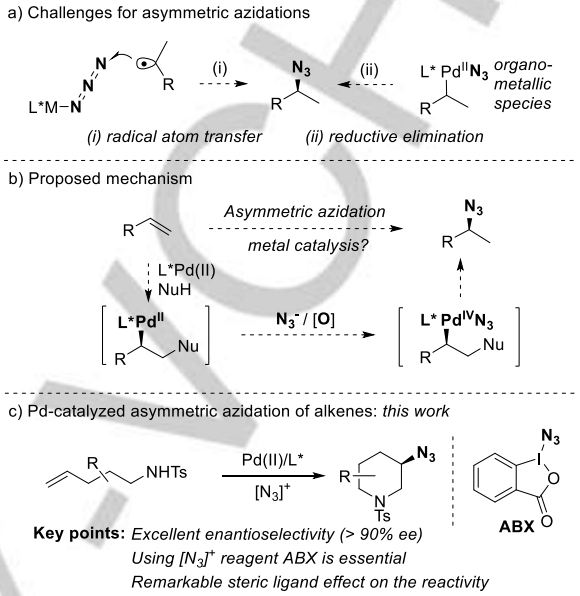


Figure 1. Representative drugs containing 3-aminopiperidines.

Optically pure organic azides have been recognized as an important synthon in organic synthesis.[5b-c] Thus, much efforts have been paid to develop new methods for their synthesis, such as asymmetric electrophilic azidation of carbonyl compounds.[7] Recently, azidation of alkenes represents one of the most efficient methods.[8]



Scheme 1. Asymmetric azidation of unactivated alkenes.

Nevertheless, asymmetric azidations are scarcely reported, and mainly rely on asymmetric Michael addition reaction of deficient alkenes by using organocatalysts (Jacobsen[9a,b] and Miller[8c-d]) or chiral Lewis acids (Feng).[10] So far, the studies on the asymmetric azidation of electro-neutral or rich alkenes are extremely limited. There is only one elegant case reported by Burns and coworkers, where the enantioselective haloazidation of allylic alcohols was accomplished by a chiral Schiff-based titanium complex.[11]

Transition-metal catalysis has been regarded as a powerful tool in asymmetric synthesis. Compared to a series of asymmetric reactions, transition-metal catalyzed asymmetric azidation is significantly retarded, which is not surprising considering the following issues: (1) although a series of azidation of unactivated alkenes have been reported via radical pathways, second or tertiary sp^3 C-N_3 bonds were generally forged through a radical atom transfer process, making asymmetric azidation extremely challenging (Scheme 1a, *i*);[12] (2) as an alternative pathway, reductive elimination of organometallic azides species, such as C-$Pd^{II}(L)_2N_3$, is a problematic step, leading to an unsuccessful catalytic azidation (Scheme 1a, *ii*);[13] and (3) owing to a strong coordination ability, excess amount of azide anion could promote chiral ligand dissociation from metal centers,[14] retarding the asymmetric azidation.

As our ongoing research interests in difunctionalizations of alkenes, we recently disclosed several palladium-catalyzed intramolecular amination of alkenes proceeding through 6-*endo* cyclization, giving various 3-substituted piperidines;[15] meanwhile, an asymmetric version has also been achieved by employing sterically hindered pyridinyl-oxazoline (Pyox) ligand. [16] Notably, for these reactions, the related C-heteroatom bonds were generated by the reductive elimination of high-valent alkyl-Pd(IV) species. Inspired by these studies, we reasoned that, if an electrophilic azidating reagent can be used as an azidating source to generate high-valent alkyl-Pd(IV)-N_3 species, the efficient catalytic azidation of unactivated alkenes by alkyl-N_3 bond reductive elimination might be feasible (Scheme 1b).[17]

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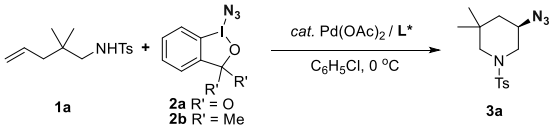
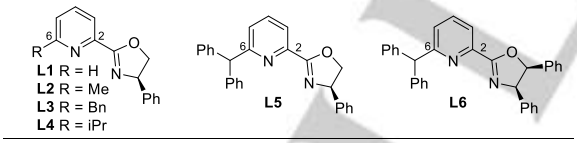
Moreover, owing to the lack of excess amount of azide anion, the asymmetric azidation might be also expected by introducing chiral ligands. Herein, we communicate a novel Pd-catalyzed enantioselective aminoazidation of alkenes proceeding through the 6-*endo* cyclization, which provides an easy access to a wide array of structurally diverse 3-azidopiperidines in good yields with excellent enantioselectivities (Scheme 1c).[18]

To test the above-mentioned hypothesis, in the presence of chiral Pd/Pyox catalysts, the reaction of **1a** was selected as the model reaction, and electrophilic reagent **2a**[19] was used as an azidating source. As shown in Table 1, the initial screening of various Pyox ligands revealed that the chiral Pyox **L1** only gave trace desired product **3a** with low enantioselectivities (entry 1). Introducing substituents into the chiral Pyox ligands at the C6 position proved to be beneficial for both reaction reactivity and enantioselectivity, and the order is **L5** > **L4** > **L3** > **L2** >> **L1** (entries 2-5). Among them, the ligand **L5** with the sterically bulkiest substituent was the best to give **3a** in 80% yield with 98% ee. The ligand **L6** bearing two phenyl groups on the oxazoline ring exhibited similar reactivities (entry 6). Decreasing the palladium catalyst loading to 5 mol% resulted in **3a** in 70% yield with 97% ee, while 2.5 mol% palladium catalyst loading led to a dramatically decreased yield (24%) with similar enantioselectivity (95% ee, entries 7-8). Moreover, the palladium catalyst exhibited poor reactivity in the absence of Pyox ligands (entry 9).

Table 1. Optimization of the Reaction Conditions.[a]



Entry	N_3 reagent	Ligand	Yield **3a** (ee)[b]
1	**2a**	**L1**	5% (32%)
2	**2a**	**L2**	27% (84%)
3	**2a**	**L3**	66% (91%)
4	**2a**	**L4**	71% (97%)
5	**2a**	**L5**	80% (98%)
6	**2a**	**L6**	76% (98%)
7[c]	**2a**	**L5**	70% (97%)
8[d]	**2a**	**L5**	24% (95%)
9	**2a**	--	10%
10	**2b**	**L5**	20% (48%)
11	$TMSN_3$ + $PhI(OAc)_2$	**L5**	0
12	**2a** + Bu_4NN_3	**L5**	0



[a]Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), chiral ligand (12 mol %), azide source (0.2 mmol) in PhCl (0.8 mL) at 0 °C for 24 hours. [b] ^1H NMR yields with CH_3NO_2 as an internal standard, and the *ee* value in parenthesis was determined by HPLC on a chiral stationary phase. Excellent regioselectivity (endo: exo > 20:1) in all cases. [c] $Pd(OAc)_2$ (5 mol %), **L5** (6 mol %).[d] $Pd(OAc)_2$ (2.5 mol %), **L5** (3 mol %).

Compared to **2a**, ether-type azidating reagent **2b** was less effective (entry 10). Moreover, when **2a** was replaced with nucleophilic $TMSN_3$ and $PhI(OAc)_2$ (PIDA), *the reaction failed to deliver product **3a*** (entry 11). Adding extraneous Bu_4NN_3 to the standard conditions also completely inhibited the reaction (entry 12). In addition, when two or more equivalents of external Bu_4NN_3 was added into a solution of (**L5**)$PdCl_2$, Pyox **L5** was completely dissociated from the palladium center (Fig. 2), thereby inhibiting the reaction (entry 10, table 1). These observations indicated that the palladium catalyst was indeed deactivated by azide anion, and the electrophilic azide reagent was essential for the asymmetric azidation. Notably, the side aminooxygenation reaction is difficult to be inhibited completely, and the reactions afforded C-O bond-forming side product in 5-16% yields (entries 2-7, for details see SI).

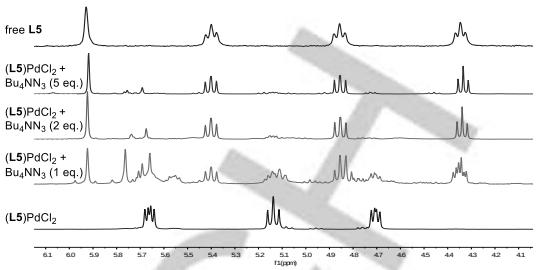
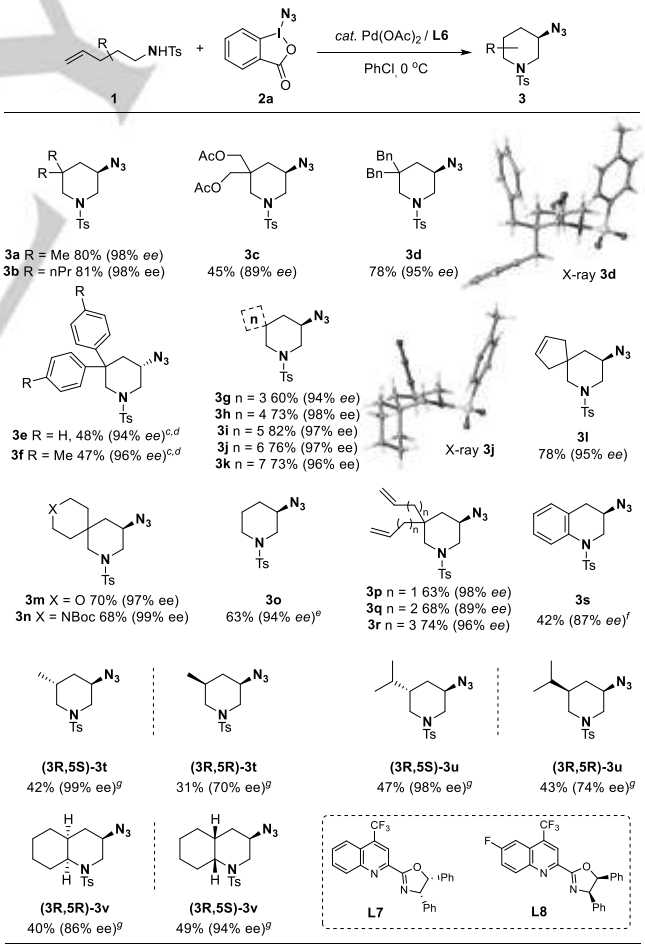


Figure 2. The reaction of the palladium complex with azide anion.

With the optimal reaction conditions in hand, the substrate scope of this transformation was then examined. Substrates with different protecting groups on the nitrogen atom were firstly surveyed, and all these substrates were suitable for the reaction to give the desired products in good yields and excellent enantioselectivities (> 90% ee), except the reaction of the substrate protected by the 2,4-DMPs or Boc group (in 9% yield or no reaction occurred, for details see SI). Then, we turned our attention to investigating various gem-disubstituted substrates. To our delight, reactions of substrates bearing different alkyl groups, such as Me (**1a**), *n*-Pr (**1b**) and Bn (**1d**), afforded the corresponding products **3a**-**3d** in good yields (78-81%) with excellent enantioselectivities (95-98% ee). Substrate **1c** bearing *gem*-diester

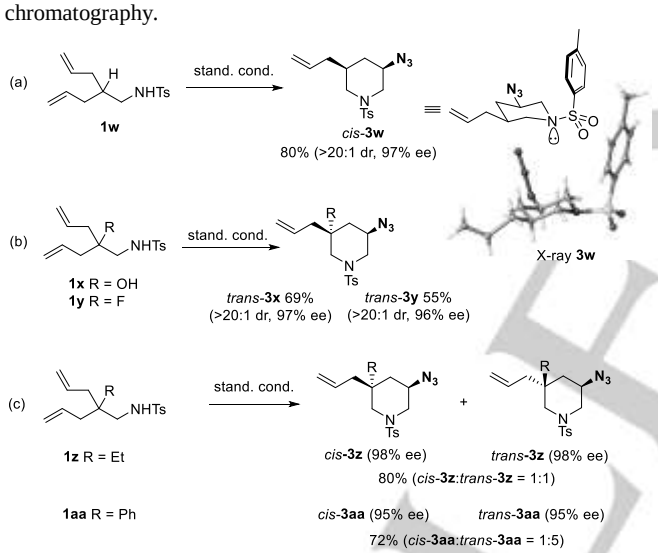
Table 2. Substrate Scope.[a,b]



[a] All reactions were conducted in 0.2 mmol with standard conidtion (entry 6 in table 1). [b] Isolated yield and *ee* determined by HPLC on chiral stationary phase; excellent regioselectivity (endo : exo >20:1) in all cases except the notice. [c] Regioselectivity, *endo*:*exo* = 8:1 ~12:1. [d] **L7** was used. alkene convertion=65%~70%. [e] **L8** was used; regioselectivity, *endo*:*exo* = 13:1. [f] Regioselectivity, *endo*:*exo* = 4:1. alkene convertion=68%. [g] the diastereoselectivity was given from crude ^1H-NMR spectra: d.r. = 1.4:1 for **3t**, d.r. = 1.1:1 for **3u**, and d.r. = 0.8:1 for **3v**.

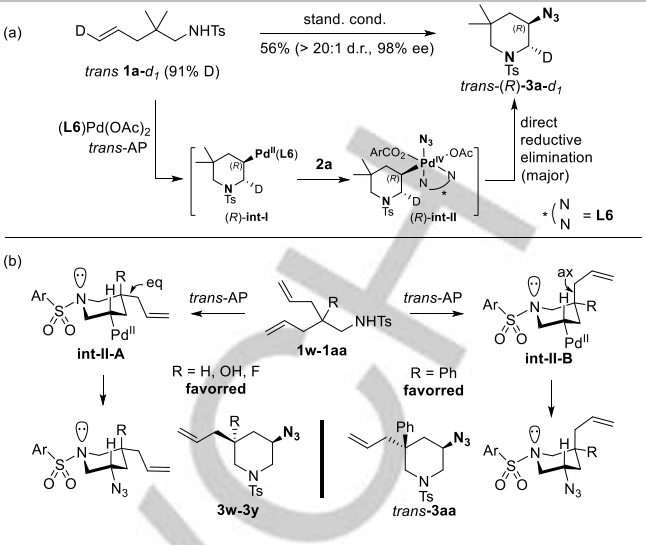
moieties ($AcOCH_2$) yielded the product **3c** with good enantioselectivity (89% ee), albeit in moderate yield (45%). For the reaction of substrates (**1e-1f**) bearing *gem*-diaryl groups, quinolinyl-oxazoline (Quox) ligand **L7** exhibited better reactivities than **L6**, giving products **3e-3f** in excellent enantioselectivities (94-96% ee) and moderate yields. Moreover, substrates with 3~7 carbon rings also reacted smoothly to deliver the *spiro* piperidine products **3g-3k** in good yields (60-82%) and excellent enantioselectivities (94-98% ee); notably, substrate bearing cyclic alkenes (**1l**) and *spiro* heteroatom-cycle substrates (**1m-1n**) were also suitable for the reaction to give the products **3l-3n** in 68-78% yields with 95-99% ee. To clarify the Thrope–Ingold effect, the reaction of non-substituted substrate **1o** was investigated, and ligand **L8** provided the desired product **3o** in 63% yield with 94% ee. The absolute configuration of **3d** and **3j** were unambiguously confirmed by X-ray analysis.

To examine the regioselectivity, substrates bearing three olefinic moieties were tested under the standard conditions, the reactions favorably yielded the six-membered products **3q-3r** exclusively in good yields (63-74%) with 89-98% ee. Moreover, the aniline substrate **1s** also was compatible with the reaction conditions to give tetrahydroquinoline product **3s** in 42% yield with 87% ee. For mono-substituted substrates, as expected, these reactions proceeded smoothly to give the corresponding products **3t-3v** as two diastereoisomers in good yields (73-91%) with excellent enantioselectivities (70-99% ee), and the two diastereoisomers could be easily separated by column chromatography.



Scheme 2. Desymmetric/asymmetric aminoazidation of alkenes.

Next, we investigated the desymmetric/asymmetric reactions of diene substrates. Interestingly, the reaction of **1w** provided the single isomer *cis*-**3w** with excellent enantioselectivity (97% ee, Scheme 2a). The absolute configuration of the products (3R,5R)-**3w** was determined by the X-ray analysis. Moreover, for the substrates with small R groups, such F and OH, the desymmetric reactions of dienes **1x-1y** proceeded very well to provide the desired products *trans*-**3x** and *trans*-**3y** as a single isomer in good yields with excellent diastereo- (dr > 20:1) and enantioselectivities (96-97%, Scheme 2b). For substrates with a larger R groups, the reactions gave two isomers. For instance, the reaction of **1z** with the ethyl group (R) provided the two isomers *cis*-**3z** and *trans*-**3z** with excellent enantioselectivities (98% ee) in 1:1 diastereoselective ratio; however, the reaction of **1aa** with the phenyl group (R) afforded a major isomeric product *trans*-**3aa** with excellent enantioselectivities (95% ee) and 5:1 diastereoselective ratio (Scheme 2c).



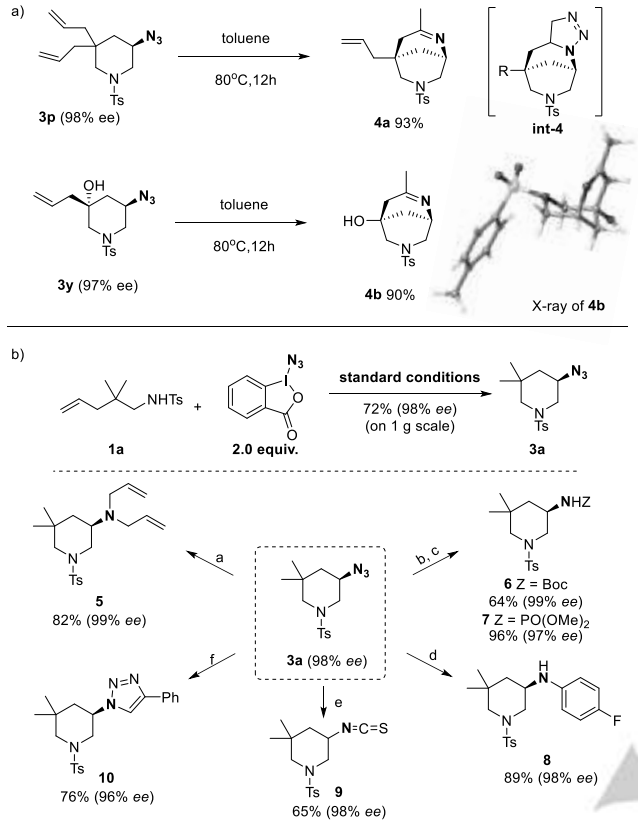
Scheme 3. Mechanistic studies of aminoazidation of alkenes.

To elucidate the different selectivities for the desymmetric reactions in Scheme 2a-2c, the stereochemistry was initially discussed. As shown in Scheme 3a, the reaction of *trans*-**1a**-d_1 provided the single product *trans*-(*R*)-**3a**-d_1 with excellent diastereo- and enantioselectivity, indicating that the reaction was initiated by an asymmetric *trans*-aminopalladation to give an enantioenriched intermediate (*R*)-**int-I**, followed by sequential oxidation and direct reductive elimination of Pd(IV) species (*R*)-**int-I**, yielding the predominated azidation (C-N_3) product, along with a small amount of oxygenation ($ArCO_2$-C bond) product. Meanwhile, it is noteworthy that the X-ray structure for **3w** showed that all the allylic, azidyl and arylsulfonyl groups were preferentially located at the equatorial orientation. Based on these observations, we assumed that two intermediates **int-II-A** and **int-II-B** would be involved in the desymmetric/asymmetric *trans*-aminopalladation of symmetric dienes **1w-1aa**. Given the 1,3-di axial interaction, the large group in **int-II** is more favored in equatorial position than the small group. The steric hindrance of hydrogen (**1w**), hydroxyl (**1x**) and fluoro (**1y**) is much smaller than that of allyl group, **int-II-A** with the allylic group at the equatorial position is much more stable than **int-II-B** with the allylic at the axial orientation. Thus, the desymmetric/asymmetric reaction of **1w-1y** proceeded via **int-II-A** exclusively, leading to the formation of products *cis*-**3w,** *trans*-**3y** and *trans*-**3y** selectively. In contrast, the steric hindrance of ethyl and allylic groups in diene **1z** is similar to each other, and the reaction generated both the **int-II-A** and **int-II-B** species, resulting in the mixture products *cis*-**3z** and *trans*-**3z**; while the phenyl group is larger than the allylic group, the **int-II-B** is more favored to form **int-II**, leading to the major product *trans*-**3aa** (Scheme 3b).

More importantly, owing to both allylic and azidyl groups at the equatorial orientation, the products **3p** and **3r** could be easily converted to the 3,6-diazabicyclo[3.3.1]nonane derivatives **4a** and **4b** in good yields, which involves a tricycle intermediate **int-4**, followed by a sequential nitrogen elimination (Scheme 4a). [20] In addition, the asymmetric azidation reaction of **1a** could be conducted on a gram scale to give product **3a** in slightly lower yield (72%) without any erosion in enantiomeric excess (98% ee, Scheme 4b), which could be efficiently transformed into alkyl amine **5** and amides **6-7**. Moreover, the enantiomerically enriched **3a** could also be converted to the related *N*-aniline product **8** in good yields. Notably, the azidyl group could undergo sequential reduction/condensation with CS_2 to provide product **9** in 65% yield with 98% ee. Lastly, triazole **10** was obtained in 76% yield with 96% ee through a click reaction of **3a** with an aryl alkyne. These examples demonstrated the applicability of this aminoazidation

reaction for the synthesis of optically pure 3-amino-piperidines as a synthon.

Scheme 4. Synthetic Applications.



Reaction conditions: (a) In, NaI, allyl bromide, r.t. (b) Pd/C (10% wt), H_2, Boc_2O, EtOAc, r.t. (c) $P(OMe)_3$, toluene, 80°C. (d) Pd/C (10% wt), H_2, CuI, 2-acetylcyclohexanone, Cs_2CO_3, 4-iodofluorobenzene, DMF, r.t. (e) PPh_3, toluene, 50°C, then CS_2, 50 °C. (f) CuI, phenylacetyene, THF, r.t.

In conclusion, we have developed the first enantioselective Pd(II)-catalyzed intramolecular aminoazidation of unactivated alkenes, which provides an easy access to a variety of enantio-enriched 3-azido piperidines in good to excellent yields with excellent enantioselectivities. In addition, employing Pyox ligand with a larger sterically bulky group is critical to the success of this process. Our current protocol represents the first example of the enantioselective alkyl C-N_3 bond formation via reductive elimination at a transition-metal center. Moreover, employing the electrophilic azidating reagent makes this catalytic amino-azidation reaction of alkenes particularly useful.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: Asymmetric azidation • Palladium-Catalyzed • Oxidative amination • Unactivated alkenes • Azidopiperidines

1 (a) A. D. Elbein, R. Molyneux, *Alkaloids: Chem. Biol. Perspect.* **1987**, *5*, 1; (b) R. J. Molyneux, L. F. James, *Mycotoxins Phytoalexins* **1991**, 637.
2 (a) K. L. Jr. Rinehart, D. Cartwright, R. A. Gardiner, *J. Am. Chem. Soc.* **1970**, *92*, 7615; (b) W. J. Gensler, M. W. Hu, *J. Org. Chem.* **1973**, *38*, 3848; (c) M. Dartmann, W. Flitsch, B. Krebs, K. Pandl, A. Westfechtel, *Liebigs Ann. Chem.* **1988**, 695.
3 (a) M. Ishikawa, D. Kubota, M. Yamamoto, C. Kuroda, M. Iguchi, A. Koyanagi, S. Murakami, K. Ajito, *Bioorg. Med. Chem.* **2006**, *14*, 2109; (b) M. Ishikawa, Y. Hiraiwa, D. Kubota, M. Tsushima, T. Watanabe, S. Murakami, S. Ouchi, K. Ajito, *Bioorg. Med. Chem.* **2006**, *14*, 2131.
4 (a) S. Kovacková, M. Dracínsky, D. Rejman, *Tetrahedron* **2011**, *67*, 1485; (b) M. Lampilas, J. Aszodi, D. A. Rowlands, C. Fromentin, US2003/199541, 2003, A1; (c) A. Ansari, R. Ramapanicker, *J. Org. Chem.* **2018**, *83*, 8161.
5 Metal-catalyzed diaminations of alkenes have been extensively studied, while the reactions generally provided *exo*-cyclization products, rather than *endo*-cyclization products. For details, see: (a) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; (b) J. Streuff, C. H. övelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; (c) K. Muñiz, C. H. Hövelmann, J. Streuff, *J. Am. Chem. Soc.* **2008**, *130*, 763; (d) Y.-F. Wang, X. Zhu, S. Chiba, *J. Am. Chem. Soc.* **2012**, *134*, 3679; (e) J. H. Conway Jr., T. Rovis, *J. Am. Chem. Soc.* **2018**, *140*, 135. For asymmetric diamination, see: (f) E. L. Ingalls, P. A. Sibbald, W. Kaminsky, F. E. Michael, *J. Am. Chem. Soc.* **2013**, *135*, 8854; (g) S. Fu, H. Yang, G. Li, Y. Deng, H. Jiang, W. Zeng, *Org. Lett.* **2015**, 17, 1018.
6 (a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297; (b) S. Bräse, K. Banert, **2009**, John Wiley & Sons; (c) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188; (d) D. Intrieri, P. Zardi, A. Caselli, E. Gallo, *Chem. Commun.* **2014**, *50*, 11440; (e) H. Tanimoto, K. Kakiuchi, *Nat. Prod. Commun.* **2013**, *8*, 1021.
7 (a) Q.-H. Deng, T. Bleith, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2013**, *135*, 5356; (b) C.-J. Wang, J. Sun, W. Zhou, J. Xue, B.-T. Ren, G.-Y. Zhang, Y.-L. Mei and Q.-H. Deng, *Org. Lett.* **2019**, *21*, 7315.
8 For reviews, see: (a) K. Wu, Y. Liang, N. Jiao, *Molecules* **2016**, *21*, 352; (b) M. Goswami, B. de Bruin, *Eur. J. Org. Chem.* **2017**, 1152; For some selective examples, see: (c) W. Kong, E. Merino, C. Nevado, *Angew. Chem. Int. Ed.* **2014**, *53*, 5078; (d) L. Xu, X. Q. Mou, Z. M. Chen, S. H. Wang, *Chem. Commun.* **2014**, *50*, 10676; (e) H. Chen, W. Yang, W. Wu, H. Jiang, *Org. Biomol. Chem.* **2014**, *12*, 3340; (f) X. Sun, X. Li, S. Song, Y. Zhu, Y. F. Liang, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 6059; (g) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069. (h) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790. (i) F.-L. Wang, X.-Y. Dong, J.-S. Lin, Y. Zeng, G.-Y. Jiao, Q.-S. Gu, X.-Q. Guo, X.-Y. Liu, *Chem* **2017**, *3*, 979.
9 (a) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959; (b) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; (c) T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem., Int. Ed.* **2000**, *39*, 3635; (d) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134; (e) H.-C. Chiu, X. Y. See, I. A. Tonks, *ACS Catal.* **2019**, *9*, 216.
10 (a) P. F. Zhou, L. L. Lin, L. Chen, X. Zhong, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2017**, *139*, 13414; (b) P. Zhou, X. Liu, W. Wu, C. Xu, X. Feng, *Org. Lett.* **2019**, *21*, 1170.
11 F. J. Seidl, C. Min, J. A. Lopez, N. Z. Burns, *J. Am. Chem. Soc.* **2018**, *140*, 15646.
12 For the selective radical azidation of alkenes forming a secondary C-N_3 bond, see: (a) Y.-A. Yuan, D.-F. Lu, Y.-R. Chen, H. Xu, *Angew. Chem. Int. Ed.* **2015**, *55*, 534; (b) J. C. Siu, G. S. Sauer, A. Saha, R. L. Macey, N. Fu, T. Chauvirie, K. L. Lancaster, S. Lin, *J. Am. Chem. Soc.* **2018**, *40*, 12511; (c) F. Wang, X. Qi, Z. Liang, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2014**, *126*, 1912.
13 F. M. Miloserdov, C. L. McMullin, M. M. Belmonte, J. Benet-Buchholz, V. I. Bakhmutov, S. A. Macgregor, V. V. Grushin, *Organometallics* **2014**, *33*, 736
14 Z. Dori, R, F. Ziolo, *Chem. Rev.* **1973**, *73*, 247.
15 G. Yin, X. Mu, G. Liu, *Acc. Chem. Res.* **2016**, *116*, 2306.
16 (a) X. Qi, C. Chen, C. Hou, L. Fu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 7415; (b) C. Chen, P. M. Pfluger, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2019**, *58*, 2392; (c) C. Hou, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2020**, *59*, 2735; (d) C. Chen, C. Hou, P. Chen, G. Liu, *Chin. J. Chem.* **2020**, *38*, 346.
17 The sp^2 C-N_3 bond formation via reductive elimination of Pd(IV) species was proposed by Jiao and coworkers. For details, see: Q. Zheng, P. Feng, Y. Liang, N. Jiao, *Org. Lett.* **2013**, *15*, 4262.

10.1002/anie.202006757

18 Racemic intramolecular aminoazidation of alkenes via radical pathways was reported, however, which afforded achiral *exo*-cyclization products, see: K. Shen, Q. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 13110.
19 (a) A. P. Krasutsky, C. J. Kuehl, V. V. Zhdankin, *Synlett*. **1995**, 1081; (b) Y. Shinomoto, A. Yoshimura, H. Shimizu, M. Yamazaki, V. V. Zhdankin, A. Saito, *Org. Lett.* **2015**, *17*, 5212; (c) G. Fumagalli, P. G. T. Rabet, S. Boyd, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11481 (d) P. G. T. Rabet, G. Fumagalli, S. Boyd, M. F. Greaney, *Org. Lett.* **2016**, *18*, 1646; (e) Y. Wang, Z. Fang, X. Chen, Y. Wang, *Org. Lett.* **2018**, *20*, 5732; (f) D. Wu, S.-S. Cui, Y. Lin, L. Li, W. Yu, *J. Org. Chem.* **2019**, *84*, 10978.
20 (a) M. E. Hermes, F. D. Marsh, *J. Org. Chem.* **1972**, *37*, 2969; (b) K. J. Shea, J. S. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 4846; (c) Y. Xu, Y. Wang, S. Zhu, G. Zhu, Y. Jia, Q. Huang, *J. Fluorine Chem.* **2000**, *106*, 133.

10.1002/anie.202006757

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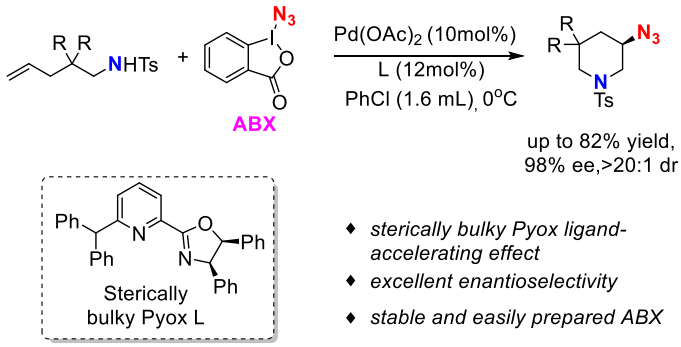

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Palladium(II)-Catalyzed Enantioselective Azidation of Unactivated Alkenes

The first Pd-catalyzed enantioselective intramolecular aminoazidation of unactivated alkenes using readily accessible 1-azido-1,2-benziodoxol-3(1H)-one (ABX) as an azidating source has been established herein, which affords a wide variety of structurally diverse 3-N_3-substituted piperidines in good yields with excellent enantioselectivities. The reaction features good functional group compatibility and mild reaction conditions. Notably, the employment of both an electrophilic azidating reagent and the sterically bulky chiral pyridinyl-oxazoline (Pyox) ligand is crucial to the successful reaction.