Communication

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Enantioselective Pd(II)-Catalyzed Intramolecular Oxidative 6-*endo* Aminoacetoxylation of Unactivated Alkenes

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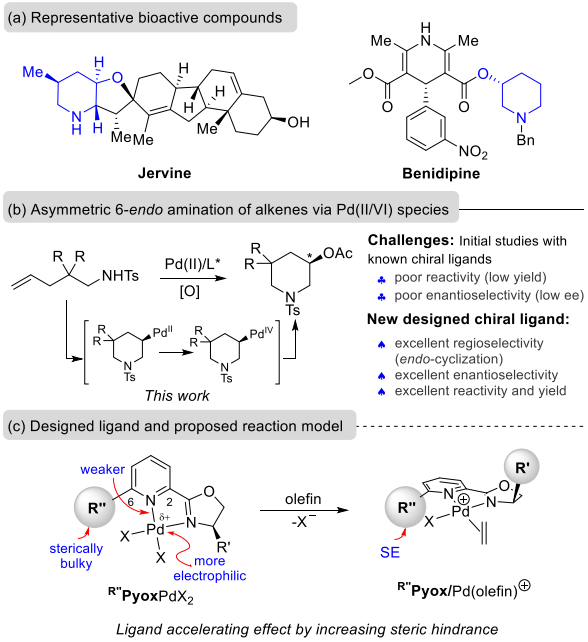
Supporting Information Placeholder

ABSTRACT: A novel asymmetric 6-*endo* aminoacetoxylation of unactivated alkenes by palladium catalysis, which yields chiral *β*-acetoxylated piperidines with excellent chemo-, regio- and enantioselectivities under very mild reaction conditions, has been established herein by employing a new designed pyridine-oxazoline (Pyox) ligand. Importantly, introducing a sterically bulky group into the C-6 position of Pyox is crucial to enhance the reactivity of the amino-acetoxylation of alkenes.

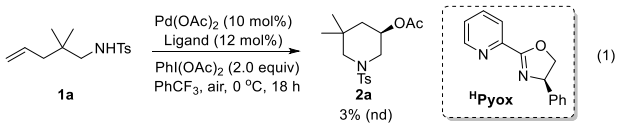
Enantiomer-enriched nitrogen-containing heterocycles, such as 3-hydroxypiperidines, are frequently found in pharmaceuticals, agrochemicals and natural products.[1] For instance, Jervine, a steroidal alkaloid, isolated from the Veratrum plant genus;[2] Benidipine, a dihydropyridine calcium channel blocker for curing hypertension (Scheme 1a).[3] Considerable efforts have been therefore directed toward synthesis of chiral heterocycles, and many methods have been developed.[4] Among them, asymmetric palladium-catalyzed intramolecular oxidative amination of alkenes is considered as the one of most prevalent strategy, which however still remains a big challenge in organic synthesis.[5] So far, some of such transformations have been achieved by the groups of Yang,[6] Zhang,[7] Stahl,[8] Michael[9] and us,[10] which underwent 5-*exo* cyclizations to provide five-membered heterocycles with high enantioselectivities. However, to the best of our knowledge, there have never been any examples of enantioselective Pd-catalyzed 6-*endo* oxidative amination of alkenes for the synthesis of chiral piperidines reported in documents to date.[11] Herein, we communicate this asymmetric palladium-catalyzed 6-*endo* oxidative aminoacetoxylation of unactivated alkenes, which provides an easy access to enantiomer-enriched 3-acetoxy piperidines. Notably, we found that a novel sterically bulky pyridinyl-oxazoline (Pyox) is very essential to achieve a highly efficient reaction with excellent regio- and enantioselectivities (Scheme 1b).

For C-heteroatom bonds that can be easily generated through reductive elimination at a Pd(IV) center, a series of palladium-catalyzed difunctionalizations of alkenes, allowing the efficient synthesis of nitrogen-containing heterocycles, have been developed.[12] In recent years, our group disclosed a series of palladium-catalyzed intramolecular oxidative amination of alkenes,[13] most of which underwent 6-*endo* aminocyclizations. For instance, Pd-catalyzed aminoacetoxylation of unactivated alkenes provided an access to the straightforward and efficient



Scheme 1. Enantioselective Pd(II)-catalyzed oxidative amination of unactivated alkenes (SE = steric effect).

synthesis of structurally diverse 3-acetoxylated piperidines with high regioselectivities.[13e] Thus, we reasoned that, if a chiral ligand could be explored to carry out the palladium-catalyzed reaction, the asymmetric 6-*endo* aminoacetoxylation of unactivated alkenes giving the chiral 3-acetoxylated piperidines might be realized (Scheme 1b). Our initial investigations started with the commonly used nitrogen-based chiral ligands, which however significantly inhibited the reaction and resulted in poor yields and low enantioselectivities (For details, see SI). Then, we turned our attention to exploring some new chiral ligands that would be helpful to enhance both reactivities and enantioselectivities.

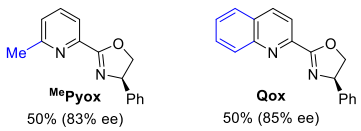


Reported examples of the oxidative amination reaction revealed that Pyox/Qox was a privileged ligand;[5-10] however, the ligand **^{H}Pyox** had a detrimental effect on the aminoacetoxylation reaction of **1a**, which was possibly attributed to the strong

electron-donator (^{H}**Pyox**) to $Pd(OAc)_2$, reducing the Lewis acidity of the palladium catalyst (eq. 1).[14] To enhance the reactivity of the palladium catalyst, we hypothesized that, if a sterically congested substituent (R") was introduced into the C-6 position of the Pyox ligand, the sterically bulky R" group makes the interaction between the pyridinyl group and the palladium center weaker, thus increasing the ^{Py}N-Pd bond length (Scheme 1c).[6c,8b] The ligated palladium catalyst will become more electronphilic, which facilitates the activation of olefins. [15,16].

Table 1. Ligand screening.[a,b]

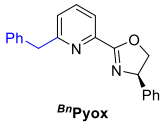
a) known ligand screening



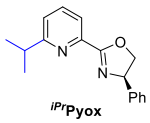
^{Me}**Pyox** 50% (83% ee)

Qox 50% (85% ee)

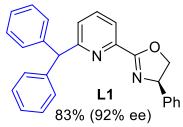
b) new designed ligand screening



^{Bn}**Pyox** 52% (91% ee)



^{iPr}**Pyox** 56% (91% ee)

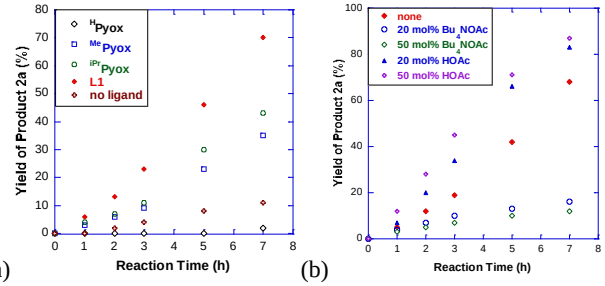


L1 83% (92% ee)
86% (90% ee)[c]
89% (87% ee)[d]

[a]The reaction of **1a** was conducted on a 0.1 mmol scale for 18 h, the reaction conditions were listed in eq 1. [b] Yields determined by ^{1}H NMR spectroscopy of the crude mixture with $MeNO_2$ as an internal standard, and the ee value in parenthesis was determined by HPLC on a chiral stationary phase. [c]AcOH (1.0 equiv). [d]AcOH (5.0 equiv).

With these hypotheses in mind, the reported ligands, ^{Me}**Pyox** and **Qox**, were examined for the reaction of **1a**. As shown in Table 1a, to our delight, the two ligands exhibited much better reactivities than ^{H}**Pyox** and gave the desired product **2a** in both 50% yields with 83% and 85% *ee*, respectively. Unfortunately, further optimizing reaction conditions failed to obtain better results and the substrate **1a** was completely consumed. Inspired by these results, several new **Pyox** ligands bearing bulky substituents (R'') at the C-6 position were synthesized and tested. Pleasingly, the ligands ^{Bn}**Pyox** and ^{iPr}**Pyox** gave the aminoacetoxylated product **2a** in slightly better yields (52% and 56%, respectively) with excellent enantioselectivities (91%). Notably, when the **Pyox** ligand was further modified by replacing the benzyl and isopropyl groups with the bulkier diphenylmethyl group, ligand **L1** exhibited much better reactivity and the product **2a** was obtained in 83% yield with 92% *ee*. Furthermore, the yield of **2a** could be further improved by adding HOAc, albeit with slightly diminished enantioselectivities.

In order to clarify the ligand effects, the reaction rates were monitored with various of ligands. As shown in Figure 1a, reactions using the ligand with a bulky group (R") exhibited a faster rate than that using the ligand bearing a small group and the order was listed as follows: **L1** > ^{iPr}**Pyox** > ^{Me}**Pyox** > ^{H}**Pyox**. Meanwhile, the X-ray structure of ($^{R''}$**Pyox**)$PdCl_2$[17] illustrated the order of ^{Py}**N**-Pd(II) bond lengths as follows: (**L1**)$PdCl_2$ (2.162 Å) > (^{Me}**Pyox**)$PdCl_2$ (2.131 Å)[18] > (^{H}**Pyox**)$PdCl_2$ (2.027 Å),[18] which is consistent with our hypotheses in Scheme 1c. These evidences revealed that increasing the size of the R" group in the $^{R''}$**Pyox** ligand could indeed weaken the ^{Py}**N**-Pd(II) bond, thus enhancing the electrophilicity of palladium catalyst for alkene activation. Moreover, the reaction rate could be accelerated by adding catalytic amounts of HOAc, but slowed down by adding Bu_4NOAc (Figure 1b).[19] We reasoned that the dissociation of an acetate from (**L1**)$Pd(OAc)_2$ could be promoted by adding HOAc to generate a cationic palladium/olefin complex, reported by Stahl and coworkers,[20] which however could be diminished in the presence of excessive acetates (Scheme 1c).[21]



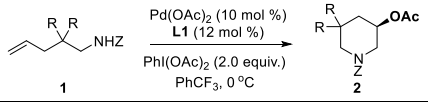
(a) (b)

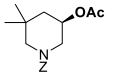
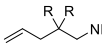
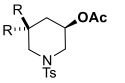
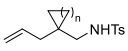
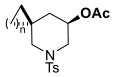
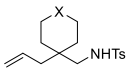
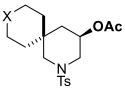
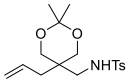
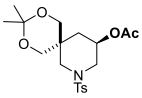
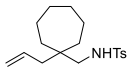
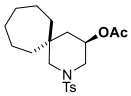
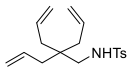
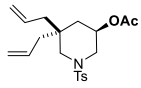
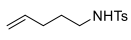
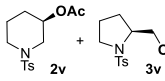
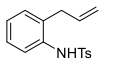
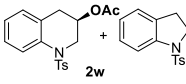
Figure 1. Ligand (a) and additive effects (b) on the reaction rate.

With the optimal reaction conditions in hand, the substrate scope of this transformation was then examined. As revealed in Table 2, different nitrogen protecting groups were firstly surveyed. Substrates with various sulfonyl groups were suitable for the transformation (see SI) and the substrate **1b** bearing the 2,4-dimethylbenzenesulfonyl protecting group gave the product **2b** in 75% yield with the best enantioselectivity (up to 95%) (entries 1-2).[22] However, the reaction of the substrate **1c** with the Boc protecting group did not occur (entry 3). Then, we turned our attention to investigating various *gem*-disubstituted substrates. To our delight, the reactions of substrates bearing different alkyl groups, such as Et (**1d**), *n*-Pr (**1e**) and Bn (**1f**), afforded the corresponding products in good yields (68-82%) and excellent ee values (88-93%, entries 4-6). Notably, a slightly decreased enantioselectivity (80%) was obtained when using the substrate **1g** containing two ester moieties (entry 7). The reactions of substrates bearing *gem*-diaryl groups (**1h-1m**), into which acetic acid was added, afforded the desired products **2h-2m** in good yields (65-86%) and excellent enantioselectivities (89-95%, entries 8-13). Furthermore, the reaction of substrates with various ring sizes also proceeded smoothly under the standard conditions to deliver the *spiro*-piperidine products **2n-2p** and **2t** in good yields (65-85%) and excellent ee values (90-92% for **2o-2p** and **2t**, 83% for **2n**, entries 14-16, 20). Substrates bearing heterocycles, such as cyclic ether (**1q**), amide (**1r**) and ketal (**1s**), were also suitable for the reaction, giving the enantiomer-enriched products **2q-2s** in good yields with good to excellent enantioselectivities (91% for **2q-2r**, 82% for **2s**, entries 17-19). Importantly, the substrate **1u** bearing three allylic moieties also worked well to yield the olefin-containing 3-acetoxyl piperidine **2u** in 48% yield with 95% ee (entry 21). It is noteworthy that a remarkable Thrope-Ingold effect was observed in this cyclization. Otherwise, poor regioselectivity will be obtained. For example, the reaction of the substrate **1v** without any additional substituents on the carbon chain gave both the *6-endo* and *5-exo* products **2v** and **3v** in 50% and 34% yields with excellent enantioselectivities (90%, entry 22). Meanwhile, a similar result was also obtained for the substrate **1w** (entry 23). Moreover, 1,1- and 1,2-disbstituted olefin substrates were ineffective for this enantioselective cyclization reaction. To demonstrate the preparative utility of this methodology, our current reaction could be performed on a 5 mmol scale without loss in reaction efficiency (entry 8). The absolute configuration of the products (R)-**2a** and (R)-**2f** were unambiguously established by X-ray analysis (Figure 2).

Next, we investigated the desymmetrization of diene substrates **4a** and **4b**. The reaction of **4a** under standard conditions delivered the two diastereoisomers *cis*-**5a** and *trans*-**5a** with excellent regioselectivities (>20:1) and enantioselectivities (88% and 95% respectively), but poor diastereoselectivities (2.5:1, Scheme 2a). Interestingly, the desymmetrization of the substrate **4b** bearing the free hydroxyl group furnished the 6-*endo* product (3*S*,5*R*)-**5b** in62% yield with >20:1 dr ratio and 98% ee (Scheme 2b).[23] These results indicated that the hydroxyl group is critical to the success

Table 2. Substrate scope.[a]



Entry	Alkene		Product		yield	ee
1		**1a** Z = Ts		**2a**	82%	92%
2		**1b** 2,4-Me$C_6H_3SO_2$		**2b**	75%	95%
3		**1c** Boc		**2c**	0	---
4		**1d** R = Et		**2d**	80%	92%
5		**1e** *n*-Pr		**2e**	82%	93%
6		**1f** CH_2Ph		**2f**	68%	88%
7		**1g** CH_2OAc		**2g**	75%	80%
8[c]		**1h** Ph		**2h**	86% (80%)[d]	93% (95%)[d]
9[c]		**1i** *p*-FC_6H_4		**2i**	82%	92%
10[c]		**1j** *p*-ClC_6H_4		**2j**	86%	95%
11[c]		**1k** *p*-$MeOC_6H_4$		**2k**	71%	92%
12[c]		**1l** *p*-MeC_6H_4		**2l**	67%	89%
13[c]		**1m** *m*-MeC_6H_4		**2m**	65%	94%
14		**1n** n = 1		**2n**	65%	83%
15		**1o** n = 3		**2o**	85%	90%
16		**1p** X = CH_2		**2p**	72%	90%
17		**1q** X = O		**2q**	83%	91%
18		**1r** NBoc		**2r**	70%	91%
19		**1s**		**2s**	72%	82%
20		**1t**		**2t**	75%	92%
21		**1u**		**2u**	48%	95%
22		**1v**		**2v** 50% **3v** 34%		90% 90%
23		**1w**		**2w** 41% **3w** 38%		81% 86%

[a]Reaction conditions: substrates **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ligand (12 mol %), $PhI(OAc)_2$ (2 equiv.), in $PhCF_3$ (0.6 mL), 0 °C for 18 h. [b]Isolated yield, and *ee* determined by HPLC on chiral stationary phase. [c]EtOAc (0.6 mL) as solvent and AcOH (5 equiv.) as addtives. [d] 5 mmol scale.

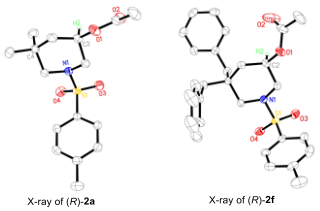
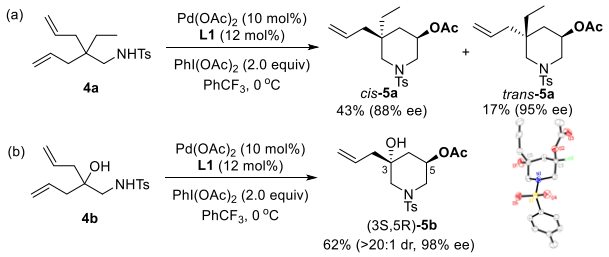


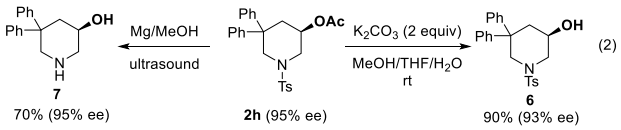
Figure 2. X-ray structure of the products **2a** (left) and **2f** (right)



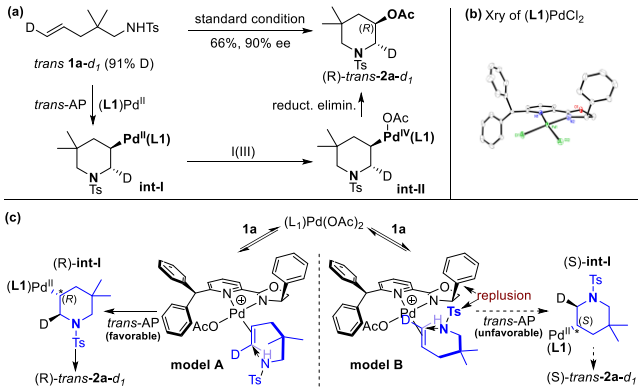
Scheme 2. The desymmetric/asymmetric aminoacetoxylation.

of the desymmetrization, which might be attributed to its coordination to the palladium catalyst.

In addition, the product **2h** could be selectively deprotected under different reaction conditions, giving the 3-hydroxy-piperidines **6** and **7** in excellent yields without the loss of ee (eq. 2).



To gain some insight into the reaction mechanism, the stereochemistry of the reaction was surveyed by employing the deuterium-labeling substrate *trans*-**1a**-d_1. Similar to the previous results, a single isomer *trans*-**2a**-d_1 was obtained, indicating that the stereoselective *trans*-aminopalladation led to an intermediate **int-I** and reductive elimination at a Pd (IV) center in **int-II** produced the C-OAc bond with stereo-retention (Scheme 3a).[24] Therefore, the 6-*endo* aminopalladation process should be an enantioselectivity-determining step.



Scheme 3. Stereochemistry and chiral model of the reaction.

To elucidate the origins of enantioselective aminopalladation step, the complex (**L1**)$PdCl_2$ was synthesized and determined by the X-ray crystallography (Scheme 3b). Steric repulsion between the phenyl group in **L1** and tosylamide in substrate caused an unfavored 6-*endo*-aminopalladation of model **B**, and the favored *trans*-aminopalladation of model **A** generated a chiral intermediate [(*R*)-**int-I**] containing C-N bond with high enantioselectivity, which affords the chiral product (R)-**2a** via a sequential oxidation and reductive elimination (Scheme 3c).[25]

In conclusion, we have developed a novel enantioselective Pd-catalyzed 6-*endo* aminoacetoxylation of unactivated alkenes, providing an easy access to structurally diverse 3-acetoxylated piperidines with excellent regio- and enantioselectivities. Moreover, we found that introducing a sterically bulky group at the C-6 position of Pyox is crucial to enhance the reactivity of palladium catalysts as well as enantioselectivities for the aminoacetoxylated products.

ASSOCIATED CONTENT

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Equal Contribution

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(19) When Bu_4NOAc (1 equiv.) was added to the standard condition, the significantly decreased enantioselectivity (73% ee, 33% yield) was observed, in which a S_N2 type reductive elimination was possibly occurred due to the extra acetate. The explanation was provided in SI, and Geier, M. J.; Aseman, M. D.; Gagne, M. R. *Organometallics* **2014**, *33*, 4353.

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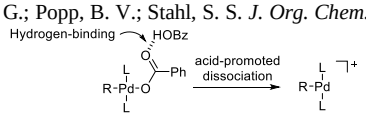


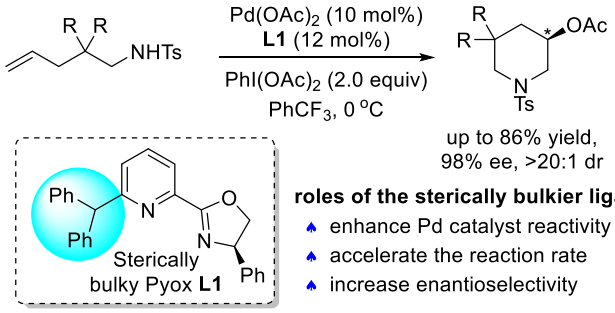
(21) Due to the generation HOAc during the catalytic cycle, the autocatalysis was observed in the Fig.1b. For the autocatalysis, see, Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc*. **2011**, *133*, 10161.

(22) For the substrates with different protecting group (Pg), the reactions gave the desired products as following: Pg = *p*-$MeOC_6H_4SO_2$, 73% yield (93% ee); Pg = *p*-^{t}Bu $C_6H_4SO_2$, 69% yield (92% ee); Pg = *p*-NO_2 $C_6H_4SO_2$, 45% yield (81% ee); Pg = *o*-NO_2 $C_6H_4SO_2$, 9% yield (81% ee); Pg = $Cl_3CCH_2OSO_2$, 24% yield (ee nd).

(23) The reaction also yielded small amounts of 5-*exo* cyclization product (10%), which was inseparable from other unidentified side products.

(24) The stereochemistry of the reaction is the same as the I(III)-mediated alkenes, but with different mechanism (ref. 11), see the SI for details.

(25) Although we cannot exclusively rule out the possibility that the reaction proceeds via an aziridinium intermediate generated from 5-*oxo-trans* aminopalladation, we favor the mechanism proposed here.



roles of the sterically bulkier ligand:

- enhance Pd catalyst reactivity
- accelerate the reaction rate
- increase enantioselectivity