OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Pd(II)-Catalyzed Asymmetric Oxidative Annulation of *N*-Alkoxyheteroaryl Amides and 1,3-Dienes

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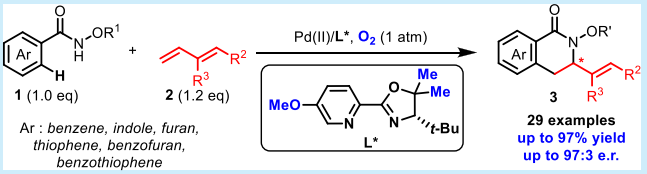
Supporting Information

ABSTRACT: The first Pd(II)-catalyzed asymmetric oxidative annulation of *N*-alkoxyaryl amides and 1,3-dienes is reported, which features particular applicability for quick assembly of different types of chiral heterocycles with high yields and enantioselectivities. A novel chiral pyridine-oxazoline bearing a methoxyl group at the C-5 position and a *gem*-dimethyl group on the oxazoline moiety was found to be crucial for conversion.



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Recent years have witnessed a rapid growth in the development of transition-metal-catalyzed transformations based on C−H activation processes.[1] Although most endeavors have focused on functionalization, addition, and cross-coupling reactions, more recently, there has been an increasing number of reports concerning formal cycloaddition processes.[2] These transformations are extremely appealing as they allow the formation of two bonds and one ring in a single step, utilizing abundant and readily available substrates containing C−H bonds. One successful example is the Pd(II)-catalyzed cascade C−H activation/allylation reaction, which employs mono-functionalized arenes and simple 1,3-dienes[3,4] as the substrates (Figure 1a).[5] Pioneered by Booker-Milburn and Lloyd-Jones,[5a] this strategy has been successfully applied to the formal annulation reactions of 1,3-dienes with a series of mono-functionalized arenes, including aryl ureas,[5a] 2-aryl cyclic-1,3-dicarbonyls and 1-aryl-2-naphthols,[5d] benzamides,[5b,e] arylphosphonic acid monoesters,[5f] and benzoic and acrylic acids.[5g] Nevertheless, developing the asymmetric variants has encountered formidable challenges. Nearly all of the racemic reactions were carried out under ligand-free conditions, as additional ligands usually drastically deactivate the catalyst. The major difficulty is finding appropriate chiral ligands and reaction conditions to keep the reactivity of the catalyst while meeting the requirements for the stereocontrol.

So far, the only successful example was developed by our group using relatively more active aryl urea as the substrate,[5h] which could form a palladacycle through C−H activation even at room temperature in the presence of a cationic Pd(II) catalyst.[6] Given the abundance of aryl amides, as well as the need for ideal methods to synthesize chiral N-heterocycles,[7] we sought to develop a Pd(II)-catalyzed enantioselective annulation of 1,3-dienes with aryl amides (Figure 1b). Although *N*-alkoxylbenzamides have been frequently investigated in Pd(II)-catalyzed C−H activation processes, related alkenylation and annulation reactions usually require high temperature (90−110 °C).[5b,8] The Pd(II)-catalyzed racemic reaction of 1,3-dienes and *N*-methoxybenzamides provides low to moderate yields and only tolerates 1,3-butadiene-1-carboxylic acid esters.[5b] As such, the enantioselective variants require the palladium/chiral ligand

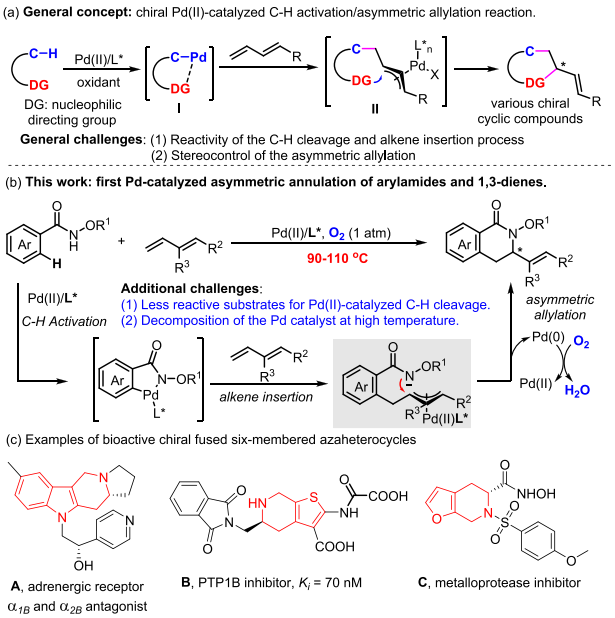

Figure 1. Palladium-catalyzed asymmetric oxidative annulation of *N*-alkoxylaryl amides and 1,3-dienes.

Received: January 17, 2019

DOI: 10.1021/acs.orglett.9b00216
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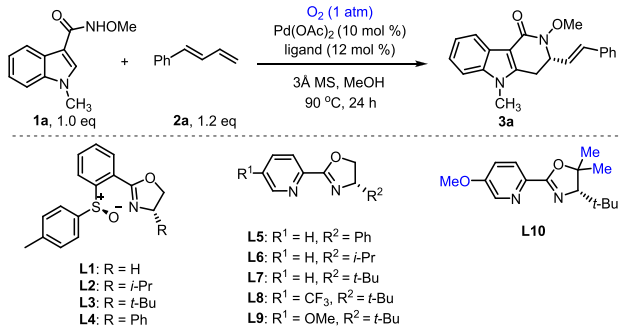
combination to have not only high activity and stereocontrol capability but also high stability to avoid the formation of palladium black at high temperature.[9] Herein, we report the Pd(II)-catalyzed asymmetric oxidative annulation of *N*-alkoxyaryl amides and 1,3-dienes using a chiral palladium catalyst bearing a novel Pyrox-type ligand,[10] which properly meets all of the aforementioned requirements. In addition to high yields, high enantioselectivities, and the use of a greener oxidant (O_2),[11] the current method also features particular applicability to assemble a variety of different types of chiral heterocycles efficiently, which are key structural motifs in many bioactive compounds. As an example, indole-fused heterocycle **A** is an adrenergic receptor α_{1B} and α_{2B} antagonist, which may find use in therapy to reduce blood pressure and promote renal blood flow.[12] Thiophene-fused chiral heterocycle **B** is a highly potent PTP1B inhibitor applicable for the treatment of type 2 diabetes and possibly obesity.[13] Similarly, furan-fused compound **C** is a potent metalloprotease inhibitor, which is potentially useful for the treatment of cancers, rheumatic diseases, and atherosclerosis.[14]

Our investigation was initiated using 3-indolecarboxylic acid derived amide **1a** and diene **2a** as the model substrates (Table 1). As the starting point, the reaction was performed without a ligand in the presence of $Pd(OAc)_2$ (10 mol %) and 1 atm of oxygen in methanol at 90 °C, providing the desired product **3a** with only 7% yield (entry 1). Rapid formation of palladium black was observed during the reaction, indicating severe decomposition of the palladium catalyst at 90 °C, which might be a major issue that causes low yield. As such, the addition of a ligand that could stabilize the palladium catalyst may solve this problem. Moreover, the chiral ligand should be capable of promoting the C−H activation process and rendering the asymmetric allylation process with high stereocontrol at the same time. Because of our previous success[5h] in the Pd(II)-catalyzed asymmetric annulation of aryl ureas and 1,3-dienes using a chiral sulfoxide-oxazoline ligand,[15] ligands **L1**−**L4** were tested, providing only up to 18% yield and up to 69.5:30.5 er. A number of chiral pyridine-oxazoline-type ligands, which have been frequently used in asymmetric Pd(II) catalysis,[10,11,16] were then evaluated for efficacy in the cascade C−H activation/asymmetric allylation reaction (entries 6−11). The results in entries 6−8 revealed that a bulky *t*-butyl group in the ligand is crucial for the stereocontrol of the reaction. Regarding the substituents on the pyridine moiety, electron-withdrawing groups have been reported to render the palladium catalyst more electrophilic and thus often deliver higher yields and enantioselectivities. Surprisingly, in this case, an electron-donating methoxyl group substituent was found superior to the electron-withdrawing group in terms of both yield and enantioselectivity (**L9** vs **L8**). In addition, adding a *gem*-dimethyl moiety on the oxazoline part[17] led to a considerable boost in both the yield and enantioselectivity (entry 11). A solvent screen revealed that protonic solvents were beneficial for the reaction, and methanol turned out to be the optimal one (see Supporting Information for details). $Pd(acac)_2$ could also promote the reaction, albeit with slightly lower yield and enantioselectivity (entry 12 vs entry 11). In the case of $Pd(TFA)_2$, which has a less basic counteranion, a significantly decreased yield was obtained with the enantioselectivity maintained (entry 13). Switching the oxidant to Ag_2CO_3 resulted in trace product formation (entry 14). Using 2,5-dimethylbenzoquinone as the oxidant also delivered satisfying results (entry 15). The reaction conditions using oxygen as the oxidant was preferred for economic reasons (entry 11).

To clarify the ligand effect of the reaction, the reaction processes were monitored with several representative ligands (Figure 2).[18] The results showed that **L9** bearing an electron-donating group led to a reaction faster thanthat of **L8** with a CF_3 substituent at the 5-position of the pyridine moiety, and **L10** bearing an additional *gem*-dimethyl moiety rendered the

Table 1. Optimization of Catalysts and Reaction Conditions[a]



entry	L	oxidant	yield (%)[b]	er[c]
1		O_2 (1 atm)	7	
2	**L1**	O_2 (1 atm)	18	62.5:37.5
3	**L2**	O_2 (1 atm)	15	0
4	**L3**	O_2 (1 atm)	9	0
5	**L4**	O_2 (1 atm)	12	69.5:30.5
6	**L5**	O_2 (1 atm)	69	72:28
7	**L6**	O_2 (1 atm)	70	73.5:26.5
8	**L7**	O_2 (1 atm)	69	90:10
9	**L8**	O_2 (1 atm)	45	88:12
10	**L9**	O_2 (1 atm)	75	93.5:6.5
11	**L10**	**O_2 (1 atm)**	**88 (90[d])**	**96:4**
12[e]	**L10**	O_2 (1 atm)	74	93:7
13[f]	**L10**	O_2 (1 atm)	50	96:4
14	**L10**	Ag_2CO_3	NR	
15	**L10**	DMBQ	87[d]	96.5:3.5

[a]Unless noted otherwise, the reaction of **1a** (0.1 mmol) and **2a** (0.12 mmol) was carried out with $Pd(OAc)_2$ (0.01 mmol), ligand (0.012 mmol), O_2 (1 atm), or oxidant (0.1 mmol) and 3 Å molecular sieves (40 mg) in MeOH (1.0 mL) at 90 °C for 24 h. [b]Based on ^{1}H NMR analysis of the crude reaction mixture using trimethylbenzene-1,3,5-tricarboxylate as an internal standard. [c]Determined by HPLC. [d]Isolated yield. [e]$Pd(acac)_2$ (0.01 mmol) was used instead of $Pd(OAc)_2$. [f]$Pd(TFA)_2$ (0.01 mmol) was used instead of $Pd(OAc)_2$.

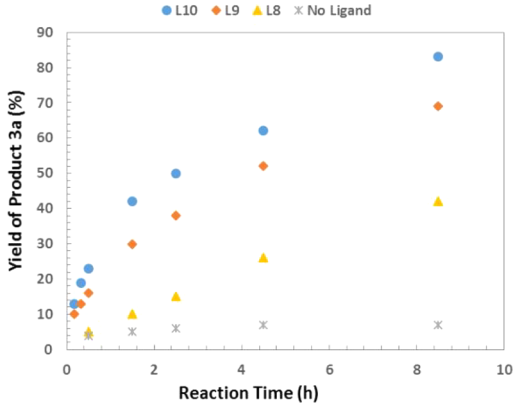


Figure 2. Ligand effect on the reaction rate.

DOI: 10.1021/acs.orglett.9b00216
Org. Lett. XXXX, XXX, XXX−XXX

reaction even faster. The ligand-free reaction almost stopped after several hours along with the quick formation of palladium black. A tentative inference on these results is that, at high temperature (90−110 °C), the decomposition of the palladium catalyst (facilitated by ligand dissociation) became a severe and major problem, and electron-rich **L9** and **L10** that bind tighter to the palladium metal would be more appropriate. At lower temperature, where the decomposition of the catalyst is negligible, electron-poor Pyrox ligands often have better reactivity.[18b,e]

With this set of conditions in hand (Table 1, entry 11), we sought to evaluate the substrate scope of the chiral Pd(II)-catalyzed cascade reaction (Figure 3). The scope of the

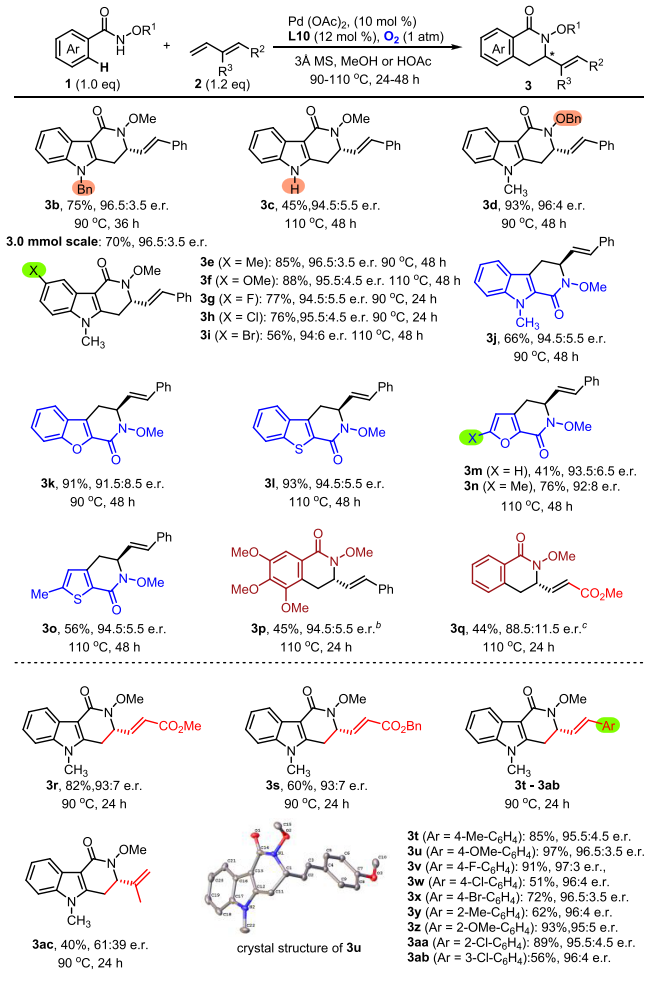
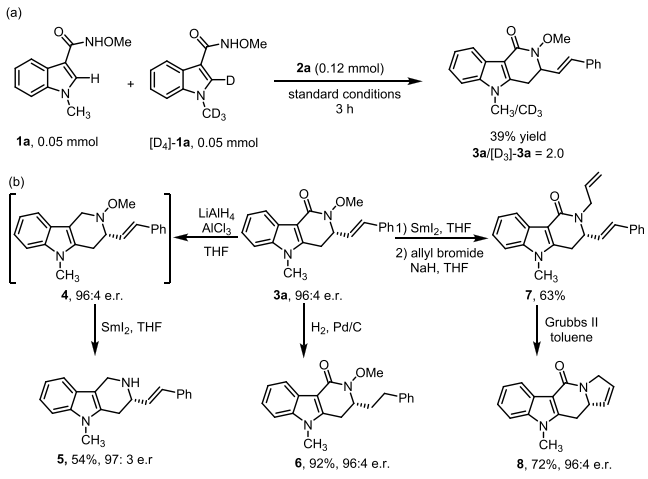


Figure 3. Substrate scope. [a]Unless noted otherwise, the reaction of **1** (0.1 mmol) and **2** (0.12 or 0.2 mmol) was carried out with $Pd(OAc)_2$ (0.01 mmol), **L10** (0.012 mmol), O_2 (1 atm), and 3 Å molecular sieves (40 mg) in MeOH (1.0 mL) at 90 or 110 °C. [b]Two-fold of the diene was used in MeOH/HOAc (0.8/0.2 mL). [c]Two-fold of the diene was used in HOAc (1 mL).

methodology was first examined in the reactions of 1,3-diene **2a** with various heterocyclic arylamides **1** at 90 or 110 °C (**3b**−**3o**). *N*-Benzyl-substituted and even an unprotected indole moiety could also be compatible for the reaction (**3b**, **3c**). To demonstrate the applicability of this method in the synthesis of fused chiral heterocycles, a gram-scale reaction of **1b** and **2a** was performed, leading to **3b** with slightly lower yield and maintained enantioselectivity. In addition to *N*-OMe amides, *N*-OBn amide could also undergo the reaction smoothly, leading to a product with excellent yield and enantioselectivity (**3d**). For 3-indolecarboxylic-acid-derived amides, either electron-donating (**3e**, **3f**) or -withdrawing (**3g**−**3i**) substituents were well tolerated. Notably, switching the amide group to the 2-position of the indole moiety also led to corresponding product with 66% yield and high enantioselectivity (**3j**). In addition to indole, amides derived from other heterocycles, such as benzofuran, benzothiophene, furan, and thiophene, were all suitable substrates, providing a variety of chiral heterocyclic products with 41−93% yields and high enantioselectivities (**3k**−**3o**). Due to lower reactivity, *N*-alkoxybenzamides were not reactive under the current reaction conditions. It has been frequently observed that the presence of acids could facilitate Pd-catalyzed C−H activation reactions.[19] As such, the solvent was changed from methanol to acetic acid. Gratifyingly, the catalyst system cause these substrates to undergo the asymmetric cascade reaction, leading to chiral isoquinolinones in moderate to high enantioselectivities (**3p**, **3q**). Next, the scope dienes were investigated for the cascade reaction (**3r**−**3ac**). Methyl 1,3-butadiene-1-carboxylate and its benzyl analogue underwent the reaction smoothly, providing the corresponding product with 93:7 er (**3r**, **3s**). Various 1-aryl-1,3-butadienes, regardless of the substitution pattern and the electronic property, were all well tolerated, affording products **3t**−**3ab** with 51−97% yields and excellent enantioselectivities. The absolute configurations of **3l** and **3u** were determined to be *S* by X-ray crystallographic analysis (see the Supporting Information for details). Isoprene, a readily available bulk chemical, despite its much lower enantioselectivity, could also undergo the asymmetric cascade reaction under the standard reaction conditions (**3ac**).

To verify the mechanism of the reaction, a same-flask intermolecular competitive reaction of **1a** and [D_4]-**1a** was performed, and a KIE value of 2.0 was observed, indicating that the C−H bond cleavage process might be the rate-limiting step (Scheme 1a). These results and literature precedents all support

Scheme 1. Isotope Labeling Experiment and Derivatization of the Products



the reaction pathway shown in Figure 1b.[5b,8,20] Moreover, to broaden the synthetic utility of the reaction, the products were subjected to further transformations. The amide moiety in **3a** could be feasibly reduced to afford *O*-methylhydroxylamine **4**, which could be further reduced by SmI_2 to amine **5**. The C−C double bond of **3a** could be readily hydrogenated to afford **6** in excellent yield. Through a reduction/allylation/ring-closing

DOI: 10.1021/acs.orglett.9b00216
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metathesis sequence, tetracyclic chiral heterocycle **8** could be obtained (Scheme 1c). The core structure of **8** resembles those bioactive molecules as exemplified by compound **A**.[12]

In conclusion, we have developed a chiral Pd^{II}-catalyzed cascade sp^2 C−H functionalization/intramolecular asymmetric allylation of *N*-alkoxyaryl amides and 1,3-dienes using oxygen as the oxidant and a novel chiral Pyrox as the ligand. The method also has particular applicability to construct various chiral heterocycles from simple starting materials efficiently, which may find wide applications for the synthesis of bioactive molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00216.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1862942 and 1898001 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from NSFC (Grant Nos. 21672197 and 21772184) and Chinese Academy of Science (Grant No. XDB20000000).

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DOI: 10.1021/acs.orglett.9b00216
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