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Regioselective Pd-Catalyzed Aerobic Aza-Wacker Cyclization for Preparation of Isoindolinones and Isoquinolin-1(2*H*)-ones

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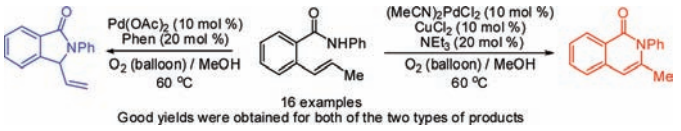
ABSTRACT



A switchable regioselective intramolecular aerobic aza-Wacker cyclization catalyzed by palladium is presented. Isoindolinones or isoquinolin-1(2*H*)-ones could be prepared selectively from the same substrates using different catalysts. The type and steric hindrance of the ligands may be the variables most significant for regiocontrol.

Nitrogen-containing heterocycles are the components of potent drugs and bioactive natural products, therefore considerable effort has been directed toward their synthesis.[1] Among the aza-cyclization reactions, oxidative aminations catalyzed by palladium represent one of the most efficient methods to build such ring systems under mild conditions.[2−4] Hegedus' pioneering work opened the study of palladium-catalyzed aza-Wacker-type reactions.[5] After further improvement, this reaction became attractive for the construction of nitrogen-containing heterocycles with dioxygen or air as the oxidant.[3,6]

As an important goal in synthetic chemistry, however, the ability to achieve catalyst-controlled regioselectivity in coupling reactions with alkenes has rarely been reported.[3a] For example, the regioselective Heck reaction has become feasible only recently.[7] A few examples of the palladium-catalyzed regioselective coupling reactions of oxygen nucleophiles with alkene substrates have also been reported.[8] In addition, several reports have described the substrate- or condition-controlled palladium-catalyzed oxidative regioselective amination of olefins.[5a,6a,9] Liu and co-workers reported the Brønsted base controlled selective preparation of five- or seven-membered nitrogen-containing heterocycles via a palladium-catalyzed intramolecular aerobic

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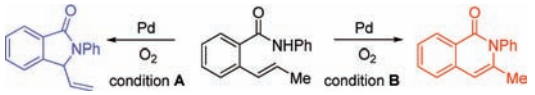
allylic oxidative amination.[10] Importantly, the Brønsted base modulated regioselective palladium-catalyzed intermolecular aerobic aza-Wacker-type reaction has been developed by Stahl and co-workers.[11] However, the *anti*-Markovnikov amination is limited in substrate scope in their reported work. Herein, we report a regioselective palladium-catalyzed intramolecular aerobic aza-Wacker cyclization. With this method, isoindolin-1-one and isoquinolin-1(2*H*)-one derivatives were prepared in different conditions and high yields (Scheme 1).

Scheme 1. Switchable Regioselective Palladium-Catalyzed Intramolecular Aerobic Aza-Wacker Cyclization



Our initial goal was to develop an enantioselective aza-Wacker-type cyclization reaction toward the total synthesis of 3-monosubstituted chiral isoindolinone natural products.[12] Although no satisfactory enantioselectivity was obtained, we discovered that different reaction conditions could provide different products, isoindolin-1-one derivative **2a** or isoquinolin-1(2*H*)-one derivative **3a** (Table 1).[13] We screened the conditions to optimize the yields of **2a** and **3a**. The well studied system, pyridine/$Pd(OAc)_2$/toluene,[6b−e] gave the best yield (68%) of **2a** in toluene under aerobic conditions (Table 1, entries 1−3). The bidentate ligand, Phen, was toxic to $Pd(OAc)_2$ in toluene and THF for the reaction yielding **2a** due to the poor solubility of the correponding palladium complex but beneficial to the catalysis in MeOH, resulting in an 85% yield of product (entries 3, 5 vs 7). An opposite behavior was observed with the quinoline as a monodentate ligand (entries 2, 4 vs 6). To our surprise, the six-membered ring **3a** was afforded as the favored product in the absence of ligand in MeOH (entry 8). The yield of **3a** could be further enhanced by adding $CuCl_2$ as the cocatalyst and changing $Pd(OAc)_2$ to $(MeCN)_2PdCl_2$ (entries 9, 10). The **3a** forming reactions in different solvents gave lower or similar yields (entries 11, 12). When 20 mol % triethylamine was added to the system described in entry 10, an excellent yield of **3a** was achieved (entry 13). In addition, $CuCl_2$ could catalyze neither of the reactions (entry 14).

To identify the variables for regiocontrol, we further screened several reaction conditions.[14] A catalytic amount of $PhCO_2H$ had no significant effect on the yield of **3a** but could decrease the yield of **2a** dramatically (entries 15, 16). This means the excess Phen in condition **A** may also function as a Brønsted base.[11] We have also studied the effect of the chloride ion (entries 7−10, 17−20). Unfortunately, maybe due to the poor solubility, no reaction happened with or without added $CuCl_2$ when $(MeCN)_2PdCl_2$ and Phen in situ formed the catalyst in MeOH (entries 17, 18). Importantly, the cocatalysts $Cu(OAc)_2$ and $Cu(OTf)_2$ could also increase the yield of **3a** (entries 19, 20). These results show that the chloride ion can improve the activity of the catalyst toward the six-membered ring product, but it is not the most significant variable for regiocontrol.[15] Similar ligands, Bpy and Phen, gave similar yields of **2a** (entries 7, 21). Interestingly, when the more sterically hindered ligand NC was used, the regioselectivity

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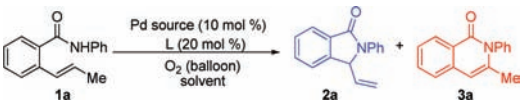
(14) Thanks for the reviewers' gentle suggestions.

was switched to the six-membered ring product, although with poor yield (entry 22). This steric effect of ligand on regioselectivity was also observed when *i*Pr-Pyox and *i*Pr-Quinox were used as ligands (entries 23−25). As a consequence of the above-mentioned, we propose that the type and steric hindrance of the ligands play key roles in regiocontrol. The poisoning effect of quinoline to $Pd(OAc)_2$ in MeOH is still unclear.

Table 1. Reaction Conditions Screening[a,b]

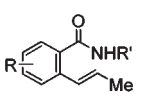
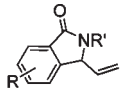
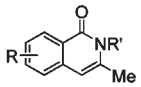
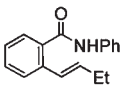
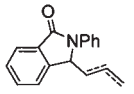
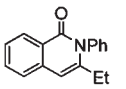
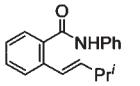
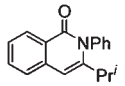
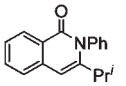
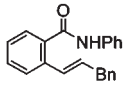
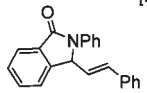
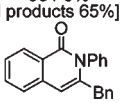
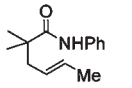
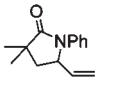
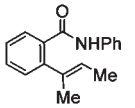
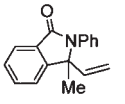


entry	Pd source	L[c]	solvent	yield (**2a**)	yield (**3a**)
1	$Pd(OAc)_2$	pyridine	toluene	68%	ND
2	$Pd(OAc)_2$	quinoline	toluene	61%	5%
3	$Pd(OAc)_2$	Phen[e]	toluene	NR	
4	$Pd(OAc)_2$	quinoline[f]	THF	51%	6%
5	$Pd(OAc)_2$	Phen[e]	THF	NR	
6	$Pd(OAc)_2$	quinoline	MeOH	NR	
7	**$Pd(OAc)_2$**	**Phen**	**MeOH**	**85%**	**ND**
8[d]	$Pd(OAc)_2$	--	MeOH	ND	9%
9[d]	$Pd(OAc)_2$[g]	--	MeOH	ND	42%
10[d]	$(MeCN)_2PdCl_2$[g]	--	MeOH	ND	85%
11[d]	$(MeCN)_2PdCl_2$[g]	--	DME	ND	74%
12[d]	$(MeCN)_2PdCl_2$[g]	--	THF	ND	84%
13[d]	**$(MeCN)_2PdCl_2$[g]**	**NEt_3**	**MeOH**	**ND**	**98%**
14[d]	--[g]	--	MeOH	NR	
15	$Pd(OAc)_2$	Phen[h]	MeOH	42%	ND
16[d]	$(MeCN)_2PdCl_2$[g]	--[h]	MeOH	ND	85%
17[d]	$(MeCN)_2PdCl_2$	Phen[e]	MeOH	NR	
18[d]	$(MeCN)_2PdCl_2$[g]	Phen[e]	MeOH	NR	
19[d]	$Pd(OAc)_2$[i]	--	MeOH	5%	32%
20[d]	$Pd(OAc)_2$[j]	--	MeOH	ND	69%
21	$Pd(OAc)_2$	Bpy	MeOH	84%	ND
22[d]	$Pd(OAc)_2$	NC	MeOH	ND	9%
23[k]	$Pd(OAc)_2$	*i*Pr-Pyox	MeOH	46[l]	ND
24[d]	$Pd(OAc)_2$	*i*Pr-Quinox	MeOH	ND	10%
25[k]	$Pd(OAc)_2$	*i*Pr-Quinox	MeOH	ND	19%

[a] Unless otherwise stated, reactions were carried out on a 0.20 mmol scale using 10 mol % Pd salt, with or without added 20 mol % ligand in solvent (2.0 mL) under 1 atm of dioxygen at 60 °C for 12 h. When the solvent was toluene, the reaction temperature was 80 °C. [b] Isolated yield. NR = No reaction. ND = trace, not detected. [c] Phen = 1,10-phenanthroline. NC = neocuproine. Bpy = 2,2′-bipyridine. *i*Pr-Pyox = (*S*)-4-isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole. *i*Pr-Quinox = (*S*)-4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole. [d] The reaction time was 15 h. [e] The corresponding complex showed poor solubility in the solvent. [f] The solubility of the corresponding complex in the solvent was not good. [g] $CuCl_2$ (10 mol %) was added. [h] $PhCO_2H$ (30 mol % for entry 15, 20 mol % for entry 16) was added. [i] $Cu(OAc)_2$ (10 mol %) was added. [j] $Cu(OTf)_2$ (10 mol %) was added. [k] The reaction time was 48 h. [l] With 49% yield of the olefin isomers of **2a** obtained; please see Supporting Information.

Based on the above results, the optimal reaction conditions leading to **2a** were found to be when using Phen as the ligand, $Pd(OAc)_2$ as the palladium source, and MeOH as the solvent and performing the reaction at 60 °C for 12 h. On the other hand, **3a** could be furnished in nearly quantitative yield with $(MeCN)_2PdCl_2$ and $CuCl_2$ as the catalytic metal sources and triethylamine as the ligand and/or base in MeOH at 60 °C for 15 h.

Table 2. Substrate Scope[a,b]

entry	substrate	condition **A**: product / yield	condition **B**: product / yield
			
R' = Ph			
1	**1a** R = H	**2a** / 85%	**3a** / 98%
2	**1b** R = 3-Me	**2b** / 76%	**3b** / 86%
3	**1c** R = 4-Me	**2c** / 77%	**3c** / 88%
4	**1d** R = 5-Me	**2d** / 97%	**3d** / 99%
5	**1e** R = 4-OMe	**2e** / 80%	**3e** / 99%
6	**1f** R = 4-Cl	**2f** / 58% (**2f** / 77% + **3f** /19%)[c]	**3f** / 49%
7	**1g** R = 5-Cl	(**2g** / 40% + **3g** / 8%)[c]	**3g** / 37%[c]
R = H			
8	**1h** R' = 4-MeC_6H_4	**2h** / 65%	**3h** / 91%
9	**1i** R' = 3,4-diMeC_6H_4	**2i** / 62%	**3i** / 85%
10	**1j** R' = 2,4-diMeC_6H_4	**2j** / 61%	**3j** / 57%
11	**1k** R' = 4-ClC_6H_4	**2k** / 87%	**3k** / 95%
12	**1l** R' = Bn	**2l** / 22%	**3l** / 84%
13	**1m** R' = Bu	**2m** / 41%[d]	**3m** / 87%[e]
14	 **1n**	 **2n** / 41% + **2n'** / 35%	 **3n** / 52% + **2n** / 5%
15	 **1o**	 **3o** / 40%[f]	 **3o** / 9%[c] [unidentified products 65%]
16	 **1p**	 **2p** / 80%	 (**3p** / 32% + **2p** / 44%)[c]
17	 **1q**	 **2q** / NR (16%)[g, c]	trace of unidentified products
18	 **1r**	 **2r** / 99%	**2r** / 27%

[a] Reaction was conducted at 0.20 mmol scale in 2.0 mL of MeOH under 1 atm of dioxygen at 60 °C. Condition **A**: $Pd(OAc)_2$ (10 mol %) and Phen (20 mol %), 12 h. Condition **B**: $(MeCN)_2PdCl_2$ (10 mol %), $CuCl_2$ (10 mol %), NEt_3 (20 mol %), 15 h. [b] All of the yields were isolated yields. [c] Reaction time was 48 h. [d] $Pd(OAc)_2$ (20 mol %) and Phen (40 mol %), 48 h. [e] Reaction time was 18 h. [f] Reaction time was 96 h. [g] The yield in parentheses was obtained under the conditions of entry 1 of Table 1.

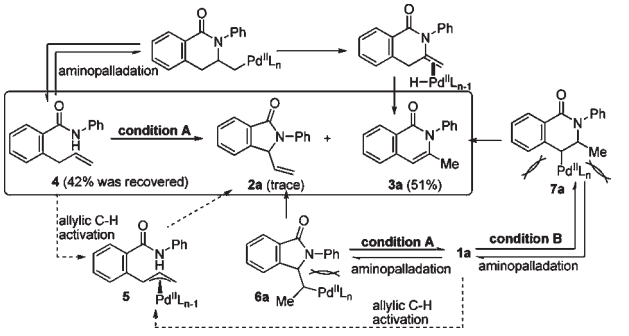
With a catalyst set identified, a variety of substrates were examined (Table 2). For substrates **1a**−**1g** (R′ = Ph), the electronic and steric properties of substituents affect the constructions of **2** and **3** in a similar manner (entries 1−7). The substrates with electron-rich groups gave better yields

(15) It has been established that the concentration of chloride ion can affect the stereochemistry of oxypalladation. For a selected recent paper and review, please see: (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (b) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038.

of **2** and **3** than the ones with an electron-withdrawing group (entries 1−5 vs 6, 7). A longer reaction time gave a better yield of **2f** (entry 6, 77% vs 58%). The *ortho*-methyl group slightly decreased the yields of both **2** and **3** (entry 2). Both of the catalyst systems tolerate different aryl substituents on the nitrogen (R = H, entries 8−11). However, the electronic effect of substituents on the benzene ring of aniline is opposite to that of R.[16] An electron-withdrawing group led to a better yield when compared with the corresponding electron-rich substrate (entry 8 vs 11). With a methyl group at the *ortho* position of aniline, cyclization of **1** under condition **B** showed an obvious decrease in yield. However, this is not the case with condition **A** (entry 10 vs 8, 9). When R′ was an alkyl group, under condition **A**, **2l** and **2m** were produced sluggishly while reactions under condition **B** occurred more rapidly to construct **3l** and **3m** (entries 12, 13). Two olefin isomers **2n** and **2n′** were obtained when substrate **1n** was catalyzed under condition **A**. Under condition **B**, a moderate yield of **3n** and 5% yield of **2n** were observed (entry 14). Substitution is not always permitted at the external vinyl position. For instance, substrate **1o** with a bulky group at this position favored the six-membered ring product **3o** under condition **A**, and substrate **1p** containing a benzyl group tended to form the five-membered ring product even under condition **B** (entries 15, 16). Substrate **1q**, with an aliphatic link instead of an aromatic functional group, showed poor reactivity toward both catalytic systems. This also occurred when using the pyridine/$Pd(OAc)_2$/toluene system (entry 17, 16% yield after 48 h at 80 °C). The trisubstituted olefin substrate **1r** has a tendency to yield **2r**, even under condition **B** (entry 18).

The **2a** forming reaction of **1a** under condition **A** may proceed through an aminopalladation/β-H elimination pathway (Wacker-type mechanism)[6m,n,17] or an allylic C−H activation/reductive elimination pathway.[8c,10,18] If the oxidative cyclization under condition **A** proceeds via an allylic oxidative substitution mechanism, both **1a** and **4** will result in the formation of the same π-allylic-Pd^{II} intermediate **5** and afford the same product **2a** (Scheme 2). If the C−N forming reaction under condition **A** follows an aminopalladation/β-H elimination pathway, the reaction of **4** will give product **3a**. The experimental results showed that **1a** favored product **2a** while **3a** was the predominant product of the reaction when using **4**. Therefore, we believe that formation of **2** from **1** under condition **A** occurs via a Wacker-type mechanism through the intermediate **6**. The six-membered ring product **3a** was obviously thermodynamically stable, but it was produced through a more sterically hindered intermediate **7a**. We propose that if a smaller ligand (MeOH, Cl^-, AcO^-) is used, the steric hindrance between the ligand and reactant in the intermediates **6** or **7** would be weaker. Thus the thermodynamic product **3a** will be produced. If a larger ligand (Phen, Bpy, *i*Pr-Pyox) is employed, the steric hindrance in **7** would be increased more than that in **6**. As a consequence, the kinetic product **2a** will be the major product. However, more sterically hindered ligands (NC, *i*Pr-Quinox) could reduce the steric hindrance difference between **6** and **7**, and then the thermodynamic product **3a** will be generated but in low yield. In the cases of substrate **1o** or **1r**, the steric hindrance difference between **6** and **7** decreased or increased, respectively. Therefore, the thermodynamic product **3o** or kinetic product **2r** was favored. A detailed mechanism study is being carried out.

Scheme 2. Oxidative C−N Forming Reaction of **4**



In summary, we have developed a palladium-catalyzed intramolecular aerobic aza-Wacker cyclization to prepare isoindolinones and isoquinolin-1(2*H*)-ones selectively from the same substrates. The switchable selectivity could be controlled by using different catalysts. We propose that the type and steric hindrance of the ligands should be the most significant variables for regiocontrol.

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Supporting Information Available. General experimental procedures and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) (a) For cyclization-decelerating effect of electron-deficient acyl group side, see: ref 6m. (b) For cyclization-accelerating effect of electron-deficient aniline side, see ref 6n.

(17) For selected recent papers, see: (a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328. (b) White, P. B.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 18594.

(18) The terminal olefins have been well studied as the substrates for palladium-catalyzed allylic oxidative substitution probably due to their high activity. For selected recent papers, see: (a) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (b) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (c) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584.