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Divergent Synthesis of Imidazoles and Quinazolines via $Pd(OAc)_2$-Catalyzed Annulation of *N*-Allylamidines

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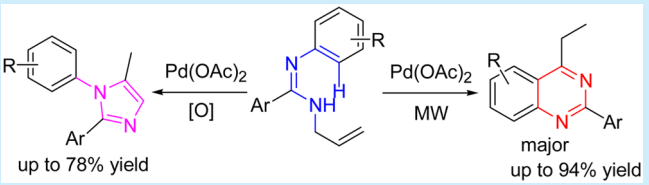
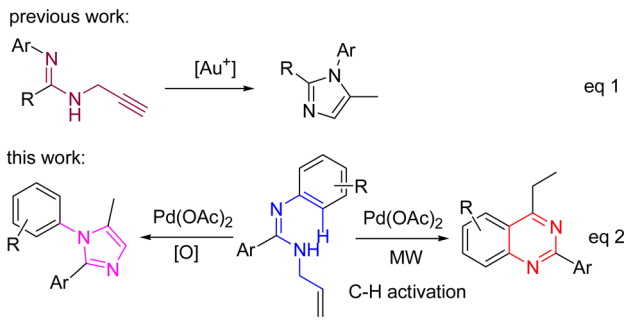
Supporting Information

ABSTRACT: A $Pd(OAc)_2$-catalyzed divergent synthesis of multisubstituted imidazoles and quinazolines from *N*-allylamidines has been developed. In the presence of oxidant O_2 from air and/or a ligand and $Pd(OAc)_2$, imidazoles were obtained. Nonetheless, under microwave (MW) irradiation in a sealed system, quinazolines as major products were produced.



Imidazoles and quinazolines are important aromatic heterocycles widely distributed in a large number of natural products and bioactive compounds.[1] They show a wide range of attractive biological properties,[2−6] such as anticancer activities[2] represented by drugs erotinib[4] and gefitinib,[6] cholinergic agonist (e.g., pilocarpine),[3] and selective adrenergic blocker prazosin.[5] Because of their importance as privileged scaffolds in drug discovery, in the past decade, significant efforts have been made on the construction of imidazoles[7] and quinazolines,[8] including annulation methods. In this context, recently, transition-metal-catalyzed intermolecular annulation of propargylamides with amines[9] and intramolecular annulation of propargylamidines[10] to form imidazole rings have been developed (Scheme 1, eq 1). Moreover, the oxidative annulation of *N*-arylmethanamidines reported by Long very recently demonstrated the potential divergent synthesis of substituted benzimidazoles and quinazolines under different conditions.[11] However, they display limited substrate scope. Furthermore, they are not applicable to the less active *N*-allylamidines.

Scheme 1. Annulation of *N*-Allylamidines



Previously, we uncovered palladium-catalyzed the annulation of simple alkenylamines.[12] As part of our continuous efforts in this area, we wish to extend the useful annulation process to other amines such as *N*-allylamidines, which can be easily prepared by the reported procedures.[13] The realization of this reaction could afford an approach to synthetically and biologically important imidazoles (Scheme 1, eq 2). However, during the course of our investigation, unexpectedly, we found that the reaction conditions were critical for the products formed. In the presence of oxidant O_2 from air and/or a ligand and $Pd(OAc)_2$, the expected imidazoles were obtained. Nonetheless, under microwave (MW) irradiation in a sealed system, quinazolines were produced as major products. Here we wish to disclose the results of the investigation.

In the initial attempt, we carried out a model reaction of *N*-allyl-*N*′-(4-methoxyphenyl)benzimidamide (**1a**) in the presence of $Pd(OAc)_2$ (20 mol %) and open air in toluene at 80 °C for 12 h, conditions similar to those used in our previous study (Table 1).[12] To our delight, the hydroamination reaction worked smoothly to give the desired imidazole **2a** in 55% yield (entry 1). Encouraged by this result, we attempted to optimize reaction conditions to improve the reaction yields. First, different palladium(II) catalysts such as $PdCl_2$ and $Pd(TFA)_2$ were screened under the same reaction conditions. $PdCl_2$ afforded the product with similar yield (45%, entry 2), while $Pd(TFA)_2$ gave poorer yield (10%, entry 3). We also found oxidant (e.g., O_2) was necessary for this reaction. No reaction took place under N_2 atmosphere at all (entry 4). Interestingly, the reaction with oxygen balloon afforded a lower yield compared with the yield obtained when air was used as oxidant (43%, entry 5). Next, effects from different ligands including phosphine and nitrogen-based ligands were tested. The results revealed that most of ligands could not improve yields (entries 6−14), except the ligand **L8**, where the yield was increased to 70% (entry 15). In terms of the catalyst loading, 20 mol % was necessary for this reaction. The reaction yield was decreased to 45% when the catalyst loading was lowered to 10 mol % (entry

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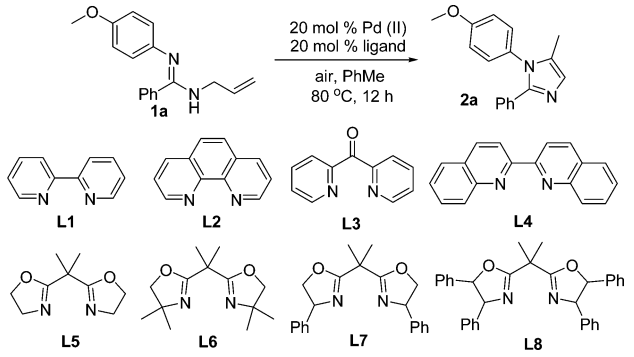
Table 1. Optimization of Reaction Conditions[a]



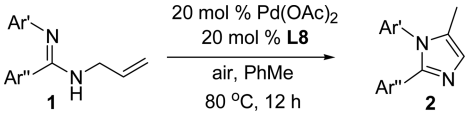
entry	cat.	ligand	yield[b] (%)
1	$Pd(OAc)_2$		50
2	$PdCl_2$		45
3	$Pd(TFA)_2$		10
4[c]	$Pd(OAc)_2$		
5[d]	$Pd(OAc)_2$		43
6	$Pd(OAc)_2$	PPh_3	31
7	$Pd(OAc)_2$	BINAP	53
8	$Pd(OAc)_2$	L1	44
9	$Pd(OAc)_2$	L2	23
10	$Pd(OAc)_2$	L3	35
11	$Pd(OAc)_2$	L4	30
12	$Pd(OAc)_2$	L5	30
13	$Pd(OAc)_2$	L6	34
14	$Pd(OAc)_2$	L7	38
15	$Pd(OAc)_2$	L8	70
16[e]	$Pd(OAc)_2$	L8	45

[a]Unless specified, a solution of the catalyst with ligand (1:1) in toluene (1 mL) was stirred at rt for 30 min, **1a** (0.1 mmol) was added, and the solution was stirred for 12 h at 80 °C. [b]Isolated yield. [c]The solution was filled with N_2. [d]1 atm of O_2 was used as oxidant. [e]10 mol % of catalyst and ligand was used.

16). Moreover, solvent screening showed that toluene was the best for this process.[14] Finally, it was found that the temperature was also important for this reaction. Heating the reaction mixture generally improved the reaction yield.

We have found the optimal reaction conditions to form imidazoles: *N*-allylamidines **1** with 20 mol % of $Pd(OAc)_2$ and ligand **L8** in toluene at 80 °C for 12 h. Next, we probed the substrate scope of this annulation process (Table 2). The reactions proceeded smoothly for a range of *N*-allylamidines (Table 2). Apparently, the reaction yields were affected by the electronic nature of the substituents on the aromatic rings. Generally, the aromatic group on nitrogen with strong electron-donating methoxy groups afforded higher yields (70−78%, entries 1−3). The amidines with less electron-donating methyl groups on phenyl ring gave lower yields (54−61%, entries 4 and 5). Steric hindrance also affected yield, as more hindered trimethoxy-substituted amidine **1f** gave lower yield (entry 6). The phenyl- and 2-naphthylamidines afforded the products with acceptable yields (entries 7 and 8). The amidine with an electron-withdrawing moiety gave a lower reaction yield (36%, entry 9). Furthermore, the electron-withdrawing moiety on the second phenyl group also affected the yield (entry 10). The amidine with both phenyl rings bearing electron-donating group gave much higher yield (77%, entry 11). However, a limitation of this process is also recognized in that amidines

Table 2. Substrate Scope of the Reaction[a]



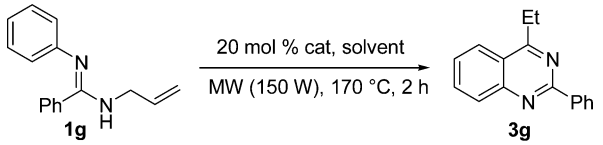
entry	Ar′, Ar″	yield[b] (%)
1	4-$MeOC_6H_4$, Ph	70 (**2a**)
2	3-$MeOC_6H_4$, Ph	72 (**2b**)
3	2-$MeOC_6H_4$, Ph	78 (**2c**)
4	4-MeC_6H_4, Ph	61 (**2d**)
5	2-MeC_6H_4, Ph	54 (**2e**)
6	3,4,5-$(MeO)_3C_6H_2$, Ph	45 (**2f**)
7	Ph, Ph	51 (**2g**)
8	2-naphthyl, Ph	49 (**2h**)
9	4-$CF_3C_6H_4$, Ph	36 (**2i**)
10	4-$MeOC_6H_4$, 4-$CF_3C_6H_4$	45 (**2j**)
11	4-$MeOC_6H_4$, 4-$MeOC_6H_4$	77 (**2k**)

[a]Unless specified, a solution of the catalyst (0.02 mmol) with ligand **L8** (0.02 mmol) in toluene (1 mL) was stirred for 30 min at rt, **1** (0.1 mmol) was added, and the solution was stirred for 12 h at 80 °C. [b]Isolated yield.

with alkyl substituents did not work under these reaction conditions.

In our exploratory studies, we found that when amidine **1g** with 20 mol % of $Pd(OAc)_2$ in 1 mL of xylenes was heated to 170 °C under microwave (MW) conditions (150 W) for 2 h unexpected quinazoline **3g** was separated as the major product in 65% yield and imidazole **2g** as the minor product (Table 3,

Table 3. Searching Optimal Reaction Conditions[a]



entry	cat	solvent	yield[b] (%)
1	$Pd(OAc)_2$	xylenes	65
2	$PdCl_2$	xylenes	48
3	$Pd(TFA)_2$	xylenes	63
4	$PdCl_2(PPh_3)_2$	xylenes	35
5	$PdCl_2$(dppf)	xylenes	23
6	$Pd(OAc)_2$	chlorobenzene	60

[a]Unless specified, a solution of **1g** (0.1 mmol) with the catalyst (0.02 mmol) in solvent (1 mL) was heated in the microwave at 170 °C for 2 h. [b]Isolated yield.

entry 1). Encouraged by this result, we then performed catalyst and solvent screening for this interesting reaction. Among a number of palladium catalysts in xylene screened for this reaction, $Pd(OAc)_2$ gave the highest yield under these conditions (entries 1−5). Chlorobenzene was tested as solvent for this reaction with no improved yield (entry 6).

Next, the scope of this new microwave-assisted annulation process for the synthesis of quinazolines was probed under the best reaction conditions (Table 3, entry 1). Studies revealed that the process serves as a general approach to structurally diverse quinazoline **3** and imidazole **2** (Table 4). It should be noted that quinazoline **3** and imidazole **2** can be separated by column directly. *N*-Allyl-*N*′-phenylbenzimidamide **1g** gave a 87% total yield of quinazoline **3g** and imidazole **2g** in 3:1 ratio

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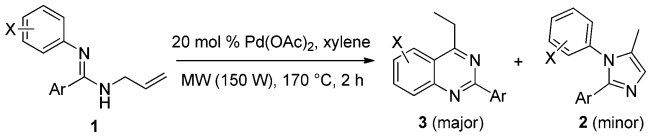
Table 4. Substrate Scope for C−H Activation[a]



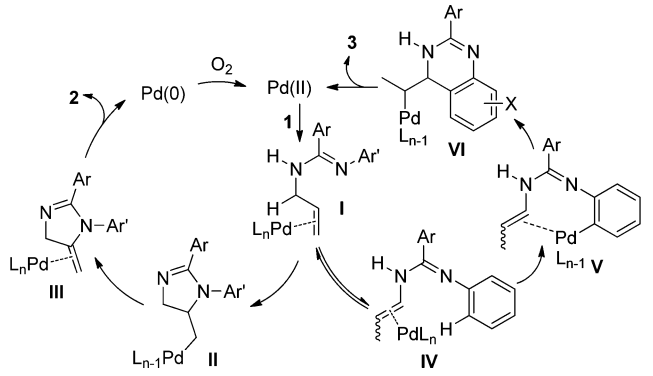
entry	X	Ar	yield[b] (%)	3:2[c]
1	H	C_6H_5	87	3.0:1 (**3g**:**2g**)
2	4-OMe	C_6H_5	90	3.7:1 (**3a**:**2a**)
3	2-OMe	C_6H_5	87	2.0:1 (**3c**:**2c**)
4	4-Me	C_6H_5	77	2.9:1 (**3d**:**2d**)
5	2-Me	C_6H_5	80	3.2:1 (**3e**:**2e**)
6	3,4,5-OMe	C_6H_5	92	1.2:1 (**3f**:**2f**)
7	3,5-OMe	C_6H_5	88	7.8:1 (**3l**:**2l**)
8	*o*-benzeno	C_6H_5	94	1.4:1 (**3h**:**2h**)
9	4-OMe	4-$CF_3C_6H_4$	86	2.8:1 (**3j**:**2j**)
10	4-OMe	4-FC_6H_4	73	1.2:1 (**3m**:**2m**)
11	4-CF_3	C_6H_5	87	0.8:1 (**3i**:**2i**)

[a]Unless specified, a solution of **1** (0.1 mmol) with the catalyst (0.02 mmol) in xylenes (1 mL) was heated in the microwave at 170 °C for 2 h. [b]Isolated yield. [c]The ratio of separated yields.

(entry 1). The substitution with a single electron-donating group on the phenyl ring of the *N*′ position gave similar results (entries 2−5). More hindered trimethoxy-substituted amidine **1f** gave excellent yield but with reduced selectivity (1.2:1, entry 6). To our surprise, *N*-allyl-*N*′-(3,5-dimethoxyphenyl)-benzimidamide **1l** afforded a high yield with good selectivity (88%, 7.8:1 of **3l**:**2l**, entry 7). *N*-Allyl-*N*′-(naphthalen-1-yl)benzimidamide **1h** had a similar result as **1f** (entry 8). The amidines with electron-withdrawing groups on the phenyl ring of benzimidamide afforded much higher total yields compared with the previous conditions to form imadazoles alone (entries 9 and 10). Finally, the amidine with electron-withdrawing moiety at the *N*′-position gave a high reaction yield but with reverse chemoselectivity, in which the imidazole product **2i** was the major product (entry 11).

The proposed catalytic cycle for the two divergent annulation reactions is described in Scheme 2. A similar pathway to pyrrole

Scheme 2. Proposed Catalytic Cycle for Annulation Reactions



formation is proposed for imidazole production.[12] First, $Pd(OAc)_2$ coordinates to the alkene of amidine **1** to give palladium−alkene complex intermediate **I**. Then a Wacker-type reaction generates Pd-alkyl intermediate **II**, followed by *β*-hydride elimination to form Pd(H)(alkene) complex **III**. Finally, a second *β*-hydride elimination and aromatization gives imidazoles **2** and Pd(0), which is oxidized by O_2 to regenerate catalyst Pd(II). While under the microwave irradiation conditions at 170 °C, the reaction probably undergoes isomerization of palladium−alkene complex intermediate **I**[15]and C−H activation[16] via presumed intermediates **IV** and **V** and leads to quinazoline product **3**. However, part of amidine **1** can follow the Wacker-type mechanism to give imidazoles **2**, observed in the process.

In summary, we have developed new palladium-catalyzed annulation processes for multisubstituted imidazoles and quinazolines from *N*-allylamidines under different conditions for the first time. Palladium-catalyzed Wacker-type reaction affords imidazoles in moderate to good yields, while palladium-catalyzed C−H activation under microwave irradiation leads to quinazolines as the major product. Further exploration of the interesting chemistry for synthesis of other heterocyclics is under investigation, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^1H and ^{13}C NMR and HRMS data for experimental procedures, and characterization of the products **2** and **3**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01435.

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Notes

The authors declare no competing financial interest.

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(14) Reaction yields in different solvents: 70% in toluene, 50% in xylene, 58% in THF, 38% in MeCN, 41% in EtOAc, 50% in EtOH, 44% in MeOH, 23% in DCM.

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