Organic LETTERS

Letter

pubs.acs.org/OrgLett

Palladium-Catalyzed Aminomethylamination and Aromatization of Aminoalkenes with Aminals via C−N Bond Activation

Lixin Li,[†,§] Peipei Liu,[†] Yijin Su,[†] and Hanmin Huang*[,†,‡]

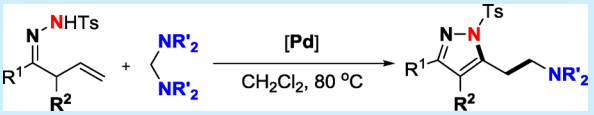
[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

[‡]Department of Chemistry, University of Science and Technology of China, Hefei, 230026, P. R. China

[§]University of Chinese Academy of Science, Beijing 100049, P. R. China

Supporting Information

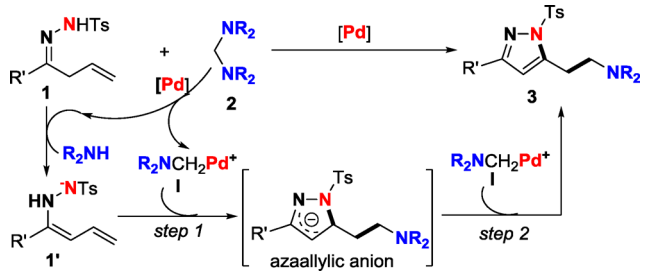
ABSTRACT: Thanks to the facile imine-enamine tautomerization, the β,γ-unsaturated hydrazones have been successfully utilized as surrogates of aminodienes for realizing the Pd-catalyzed tandem aminomethylamination/aromatization reaction with aminals via C−N bond activation. This direct and operationally simple protocol provides a fundamentally novel strategy to synthesize aromatic heterocycles from alkenes in the absence of external oxidant and base. Mechanistic studies suggested that aminal not only functioned as an aminomethyl source but also acted as formal oxidant and inner base to promote the aromatization.



N-Heterocycles hold a vital position in modern organic chemistry due to their ubiquity in nature and serve as a class of most important molecules in medical and life sciences.[1] As a result, there has been a long-standing interest in the development of direct synthetic approaches to N-heterocycles. In this respect, the palladium-catalyzed cyclization of aminoalkenes established by combining the selective C−C and C−N bonds formation reactions has evolved into a powerful strategy for the synthesis of structurally diverse N-heterocycles.[2] However, aromatic halides or super stoichiometric amounts of oxidants are required to initiate and sustain the Pd-catalytic cycle, and thus, a large amount of waste is formed. Moreover, the viability to prepare aromatic heterocycles via these methods remains a challenge.[3]

In the palladium catalysis, the reactive organopalladium species cooperative with efficient bond-formation strategy plays pivotal roles for establishing catalytic new reactions.[4] The discovery of a new and versatile organopalladium species, such as an active Pd−C and Pd−N species, often revolutionizes the catalytic performance in terms of reactivity, selectivity, and productivity.[5] Cognizant of both this goal and the ideal of green chemistry, we recently have invented a unique electrophilic cyclopalladated complex **I** benefited from the newly developed C−N bond activation of aminals (Scheme 1).[6] Unlike the well-established oxidative addition processes for generation of ArPdX species from aromatic halides,[4] the released R_2N^- from the oxidative addition reaction of aminal with Pd(0) not only could be used as a nitrogen-nucleophile for enabling a C−N bond formation process, but also might act as strong base to promote some new reaction processes. Thus, a number of catalytic new reactions have been established with this Pd-alkyl species as a leading complex.[6] Very recently, we have developed an asymmetric intermolecular aminomethylamination reaction of 1,3-conjugated dienes with aminals led by this Pd-alkyl species, where the π-allylic palladium intermediate was facilely formed and trapped by the amino moiety released from the C−N bond activation process to furnish the desired 1,3-diamines.[6g] It would be therefore of interest to explore a cyclization reaction between aminodienes and aminals based on this concept in which the π-allylic palladium intermediate would be alternatively captured by the tethered nitrogen-nucleophile in intramolecular manner. Given the facile imine-enamine tautomerization, β,γ-unsaturated hydrazones could be viewed as the surrogates of 1,3-conjugated dienes with amine functionality.[7] Inspired by this inherent feature of β,γ-unsaturated hydrazone, we envisaged that it might act as a suitable substrate to accomplish the above idea. We anticipated that aminodiene **1′** would be formed and then reacted with Pd-complex **I** to give a reactive azaallylic anion under basic reaction conditions.[8] Due to its high reactivity, the azaallylic anion can be trapped by electrophilic Pd-complex **I** again to give the target aromatic β-aminoethylpyrazoles via nucleophilic substitution and β-hydride elimination (Scheme 1).

Scheme 1. Aminomethylamination/Aromatization of β,γ-Unsaturated Hydrazones with Aminals via C−N Bond Activation



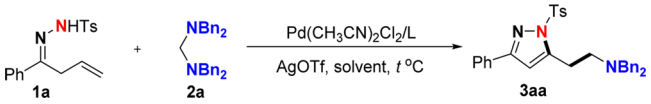
Received: October 6, 2016

DOI: 10.1021/acs.orglett.6b03001
Org. Lett. XXXX, XXX, XXX−XXX

Herein, we reported a palladium-catalyzed cascade amino-methylamination/aromatization reaction of β,γ-unsaturated hydrazones with aminals via C−N bond activation. Such reaction would be particularly valuable for the synthesis of bioactive pyrazoles, which would also provide a great opportunity to accelerate biological and biosynthetic studies of β-amino-ethylpyrazoles.[3,9,10]

Our investigations began with the reaction of (*E*)-4-methyl-*N*′-(1-phenylbut-3-en-1-ylidene)benzenesulfonohydrazide (**1a**) and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**) in CH_3CN at 120 °C with $Pd(CH_3CN)_2Cl_2$ as a catalyst precursor. After an extensive screening of the phosphine ligands, DPPP stood out as the best ligand for delivering desired product **3aa** in 65% yield. The structure of **3aa** was unambiguously confirmed by NMR spectroscopy and X-ray diffraction analysis.[11] Inspired by this promising lead, we next sought to improve the efficiency of the reaction. Among the solvents tested, CH_2Cl_2 was the best, though the reaction was also compatible with common organic solvents (Table 1, entries 12−16). The yield decreased to 70%

Table 1. Screening of Reaction Conditions[a]



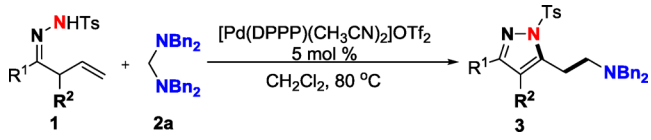
entry	ligand	solvent	*t* (°C)	yield (%)[b]
1	DPPM	CH_3CN	120	8
2	DPPE	CH_3CN	120	43
3	DPPP	CH_3CN	120	65
4	DPPB	CH_3CN	120	50
5	DPPPen	CH_3CN	120	37
6	DPPHex	CH_3CN	120	22
7	Xantphos	CH_3CN	120	17
8	DPEphos	CH_3CN	120	15
9	DPPF	CH_3CN	120	39
10	PPh_3	CH_3CN	120	40
11	PCy_3	CH_3CN	120	6
12	DPPP	CH_2Cl_2	120	78
13	DPPP	toluene	120	69
14	DPPP	*i*-PrOH	120	29
15	DPPP	DMF	120	12
16	DPPP	THF	120	49
17	DPPP	CH_2CI_2	100	76
18	DPPP	CH_2CI_2	80	70
19[c]	DPPP	CH_2Cl_2	80	86
20[d]	DPPP	CH_2Cl_2	80	42

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [Pd] (3.0 mol %), ligand (3.6 mol %), AgOTf (6.0 mol %), solvent (1.5 mL) for 12 h. [b]Isolated yield. [c][Pd] (5.0 mol %), DPPP (6.0 mol %), AgOTf (10 mol %), 24 h. [d]$Pd_2(dba)_3$ (2.5 mol %), DPPP (6.0 mol %), HOTf (6.0 mol %), 24 h.

when the reaction was carried out at 80 °C in CH_2Cl_2, but the loss of yield could be offset by increasing the catalyst loading and prolonging the reaction time to 24 h (Table 1, entry 19). The reaction could proceed with $Pd_2(dba)_3$ as the palladium source in the presence of DPPP, suggesting that Pd(0) was involved in the present reaction (Table 1, entry 20). As expected, almost the same yield (84%) of **3aa** was gained when the cationic $[Pd(DPPP)(CH_3CN)_2]OTf_2$ was utilized as catalyst (the structure of the catalyst was confirmed by X-ray analysis).[11] Finally, no desired product was detected in the absence of palladium catalyst under otherwise identical reaction conditions.

To explore the scope of this palladium-catalyzed aromatization process, various β,γ-unsaturated hydrazones were coupled with aminal **2a** under the optimized reaction conditions (Table 2). As

Table 2. Substrate Scope of Hydrazone[a]



entry	R^1	R^2	3	yield (%)[b]
1	C_6H_5	H	**3aa**	84
2[c]	2-FC_6H_4	H	**3ba**	68
3	3-FC_6H_4	H	**3ca**	75
4	4-FC_6H_4	H	**3da**	81
5	4-$CF_3C_6H_4$	H	**3ea**	80
6	4-ClC_6H_4	H	**3fa**	79
7	3,4-$Cl_2C_6H_3$	H	**3ga**	79
8	3-BrC_6H_4	H	**3ha**	77
9	4-BrC_6H_4	H	**3ia**	83
10	3-MeC_6H_4	H	**3ja**	77
11	4-MeC_6H_4	H	**3ka**	72
12[c]	2-$MeOC_6H_4$	H	**3la**	57
13	3-$MeOC_6H_4$	H	**3ma**	81
14	4-$MeOC_6H_4$	H	**3na**	80
15	3,5-$(MeO)_2C_6H_3$	H	**3oa**	83
16	2-naphthalene	H	**3pa**	80
17	2-thiophene	H	**3qa**	72
18	3-indole	H	**3ra**	75
19[c]	*i*-Pr	H	**3sa**	60
20[c]	*t*-Bu	H	**3ta**	77
21[c]	Cy	H	**3ua**	56
22	C_6H_5	Me	**3va**	36

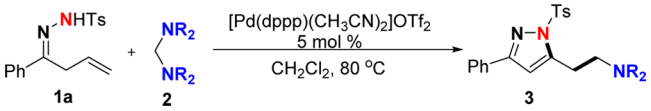
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $[Pd(DPPP)(CH_3CN)_2]OTf_2$ (5.0 mol %), CH_2Cl_2 (1.5 mL), 80 °C, 24 h. [b]Isolated yield. [c]100 °C.

shown in Table 2, both electron-rich and electron-withdrawn hydrazones showed high reactivity to afford the corresponding desired products in moderate to good yields. The electronic factor has negligible effect on this transformation, as strongly electron-withdrawing substituents or donating groups like $-CF_3$ and −OMe gave their corresponding products in good to excellent yields. However, the steric factor has a negative impact on the reaction, as aryl hydrazones with electron-withdrawing or electron-donating substituents at the *ortho* position of the phenyl ring showed lower reactivities. To our delight, raising the temperature to 100 °C, the corresponding functionalized pyrazoles could be obtained in moderate yields (Table 2, entries 2 and 12). Significantly, both meta- and para-substituted hydrazones were converted into the desired products in good yields. Disubstituted hydra-zones underwent the cyclization-aromatization quite well (Table 2, entries 7 and 15). In addition, both 2-naphthalene-substituted hydrazone and heteroaromatic hydrazones, such as 2-thiophenehydrazone and Boc-protected 3-indolehydrazone, participated in the present reaction well to give the corresponding pyrazoles in good yields (Table 2, entries 16−18). Gratifyingly, moderate to good yields (56−77%) were obtained when the reaction conducted with aliphatic ketone derived hydrazones (Table 2, entries 19−21). The reaction of **1v** with a methyl group at the α-position was found to yield cyclization product **2va** in 36% yield.

DOI: 10.1021/acs.orglett.6b03001
Org. Lett. XXXX, XXX, XXX−XXX

Next, we explored the scope and limitation of this cascade process for various substituted aminals with (*E*)-4-methyl-*N*′-(1-phenylbut-3-en-1-ylidene)benzenesulfonohydrazide (**1a**) as shown in Table 3. Irrespective of the electronic nature of the

Table 3. Substrate Scope of Aminals[a]



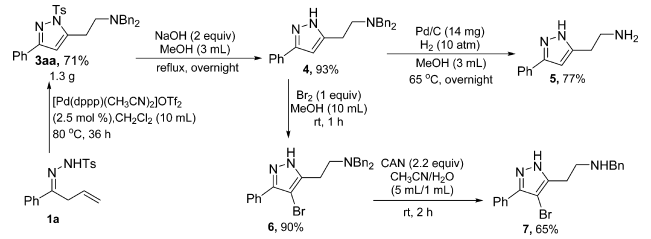
entry	R	3	yield (%)[b]
1	$C_6H_5CH_2$	**3aa**	84
2	4-$FC_6H_4CH_2$	**3ab**	71
3	4-$CF_3C_6H_4CH_2$	**3ac**	75
4	3,5-*t*-$BuC_6H_3CH_2$	**3ad**	62
5	CH_3CH_2	**3ae**	33
6	$CH_3CH_2CH_2$	**3af**	43
7	-$CH_2CH_2OCH_2CH_2$–	**3ag**	42

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [Pd(DPPP)$(CH_3CN)_2$]OTf_2 (5 mol %), CH_2Cl_2 (1.5 mL), 80 °C, 24 h. [b]Isolated yield.

substituents in the phenyl-ring of benzylamine derived aminals, the reactions performed well to give the corresponding products in good yields. Several aminals derived from simple alkylamines, such as Et_2NH and *n*-Pr_2NH, were also compatible with this process to afford the desired products **3ae**–**3af** in moderate yields. Moreover, aminal **2g** derived from cyclic amine could also be used as a coupling partner, giving the corresponding product **3ag** in good yield.

The reaction could be performed on a gram scale with good yield even at a lower catalyst loading (2.5 mol %), providing 1.3 g of **3aa** in 71% yield (Scheme 2). The Ts group of **3aa** could be

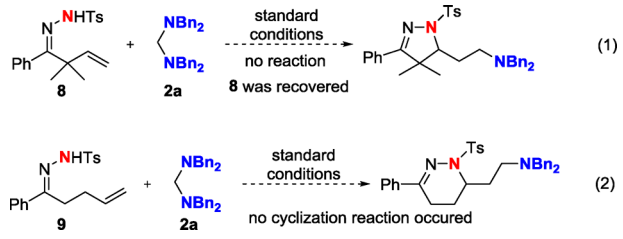
Scheme 2. Synthetic Utility of the Functionalized Pyrazoles



easily removed under mild conditions to give **4** in excellent yield. The two benzyl groups in **4** were removed to give **5** via Pd/C-catalyzed hydrogenolysis with H_2. Furthermore, compound **4** was rapidly brominated with Br_2 to give **6** in 90% isolated yield. One benzyl group in **6** was selectively removed to give **7** by treatment with CAN in CH_3CN/H_2O at room temperature. The products **5** and **7** are derivatives of Betazole, a powerful gastric secretory stimulant in medicinal chemistry,[9] suggesting that the current protocol for synthesis of *β*-aminoethylpyrazoles might find broad application in medicinal chemistry.

To gain insights into the possible mechanism of this process, several experiments were conducted under the standard conditions (Scheme 3). First, an in situ NMR experiment for investigation of the reaction of **1a** with **2a** was conducted in J-Young-type NMR tube. The ^{1}HNMR spectra revealed that desired product **3aa** together with Bn_2NCH_3 was simultaneously produced in almost 1:1 ratio when the reaction was conducted in

Scheme 3. Control Experiments



$CDCl_3$ at 80 °C (see Supporting Information). This result suggested that one molecule of Bn_2NCH_2 moiety was converted into Bn_2NCH_3, thus indicating reductive elimination of Bn_2NCH_2PdH was most likely involved in the catalytic cycle of the present reaction and aminal might act as a formal oxidant to promote the aromatization. The substrate bearing two germinal methyl groups at the *α*-position was reported to proceed as a kinetically favorable cyclization due to Thorpe–Ingold effect.[12] Therefore, **8** was tested as a substrate in the current reaction. To our surprise, no reaction took place, and the substrate **8** was recovered unchanged, which might indicate that the process of aminopalladation did not take place under the present reaction conditions. Furthermore, when (*E*)-4-methyl-*N*′-(1-phenylpent-4-en-1-ylidene)benzenesulfonohydrazide **9**, which could be potentially converted into six-membered heterocycles via aminopalladation, was also examined under the standard conditions. As expected, no desired cyclization reaction occurred, indicating that the aminopalladation/reductive elimination pathway was ruled out. These results confirmed our hypothesis that the reactive hydrazones had to be transferred to the corresponding 1,3-dienes via imine–enamine tautomerization, and the reaction was most likely initiated via migratory insertion of diene with the cyclopalladated complex **I**.

Although the mechanistic details are not clear at this stage, on the basis of the present results and precedent reports,[6] a plausible reaction pathway was proposed (Figure 1). After formation of

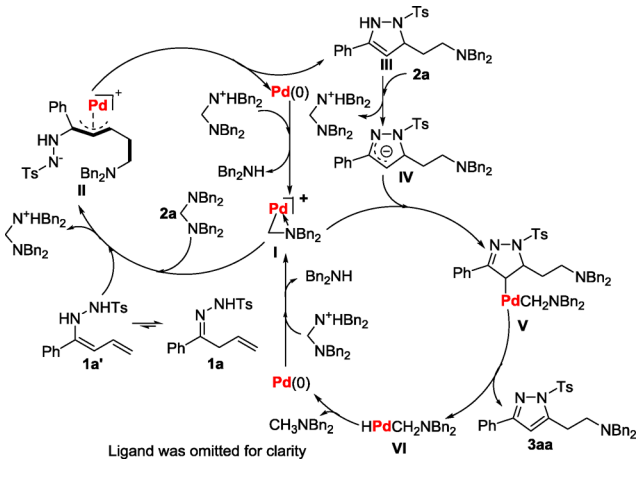


Figure 1. Plausible reaction mechanism.

the active palladium(0) species, oxidative addition of the protonated aminal takes place to form the cyclopalladated complex **I**. Then migratory insertion of double bond of the diene **1a**′ (generated in situ from **1a** via imine–enamine tautomerization) into the C–Pd bond of **I** affords the key *π*-allylic palladium intermediate **II**. The species **II** undergoes an intramolecular nucleophilic addition to give rise to intermediate **III** together

DOI: 10.1021/acs.orglett.6b03001
Org. Lett. XXXX, XXX, XXX–XXX

with regeneration of palladium(0) to furnish the first aminomethylamination catalytic cycle under the basic conditions. Deprotonation of **III** with another molecule of aminal forms the azaallylic anion **IV**,[8b] which is captured by the electrophilic cationic Pd-complex **I** again to give the species **V**. Finally, β-hydride elimination from **V** releases the desired product **3aa** together with **VI**, which undergoes reductive elimination to give Bn_2NCH_3 and regenerates Pd(0) species, thus completing the catalytic cycle.

In summary, we have developed the first palladium-catalyzed aminomethylamination/aromatization of β,γ-unsaturated hydrazones with aminals via C−N bond activation, leading to a variety of substituted β-aminoethylpyrazoles that are of interest in medicinal chemistry. The present reaction provides a new strategy to construct aromatic heterocycles from aminoalkenes in the absence of external oxidant and base under the palladium catalysis. Mechanistic studies suggest that the aminal not only acts as an aminomethyl group source but also functions as an internal base and formal oxidant to promote the aromatization. This inherent unique character of aminals and the cyclopalladated complex promise a broad perspective in many other reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03001.

Experimental procedures and compound characterization (PDF)

Full spectroscopic data for compound **1e** (CIF)

Full spectroscopic data for $[\mathbf{Pd(dppp)(CH_3CN)_2}](\mathbf{OTf})_2$ (CIF)

Full spectroscopic data for compound **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanmin@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the CAS Interdisciplinary Innovation Team, the National Natural Science Foundation of China (21133011 and 21672199).

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(11) CCDC 1498309 (**3aa**), 1498307 (**1e**), and 1498311 ($[Pd(DPPP)_2(CH_3CN)_2](OTf)_2$ contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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DOI: 10.1021/acs.orglett.6b03001
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