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Synthesis of Tetrahydropyridazines *via* Pd-Catalyzed Carboamination of Alkenyl Hydrazones

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Abstract. We report herein a facile approach to tetrahydropyridazines, containing a scaffold found in many natural products and biologically active entities, *via* Pd-catalyzed carboamination of readily available alkenyl hydrazones with aryl and alkenyl halides. Preliminary studies showed its promise for enantioselective synthesis. This work offers an expedient access to the tetrahydropyridazine scaffold bearing a variety of substitution patterns, thus significantly increasing the availability of these derivatives for downstream evaluation.

Keywords: palladium catalysis; carboamination; hydrozone; aminopalladation

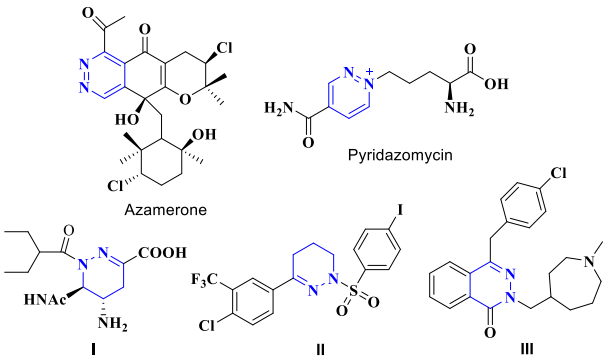

Figure 1. Example of pyridazines and tetrahydropyridazine derivatives in natural products and bio-active molecules.

Pyridazines and tetrahydropyridazines are important structural units present in natural products (e.g. Azamerone[1] and Pyridazomycin[2]) and play important pharmacological roles in a large number of biologically active molecules and pharmaceuticals (Figure 1), such as influenza neuraminidase inhibitor (e.g., **I**),[3] nonsteroidal progesterone receptor (e.g., **II**),[4] and Azalestine (e.g., **III**).[5] Pyrazine and its derivatives are considered one of the most promising heterocyclic frameworks in small molecule drug design.[5,6] Therefore, the development of efficient protocols to expand synthetic avenues for pyrazine and its derivatives is highly desirable. Protocols to synthesize these privileged structures include aza-Diels-Alder reactions of 1,2-diaza-1,3-dienes,[7] radical cyclization,[8] hydrogenation,[9] base-mediated anionic cyclization,[10] etc.[11] (Scheme 1a). Despite these advances, most of these methods are not amenable to broad generality or asymmetric synthesis due to the intrinsic limitation of the reaction patterns. Therefore, the development of alternative methods complementing the scope of extant methods are still in high demand.

The Pd-catalyzed heterocyclization reaction constitutes a fruitful platform for the construction of various O- and N-heterocycles *via* assembly of readily available organic halides and functionalized alkenes.[12] In this context, N-heterocycle-forming processes involving alkene aminopalladation have witnessed significant progress.[12c,f] In particular, highly enantioselective variants have also been developed to access several types of N-heterocycles.[13] In this context, we envisioned a straightforward access to tetrahydropyridazines by a Pd(0)-catalyzed cyclization–coupling reaction of readily available γ,δ-alkenyl hydrazone with organohalides.[14] Herein we report that the reaction proceeds with a broad substrate scope and good functionality tolerance, offering a facile assembly of a dihydroazine library (Scheme 1b).

We started by examining the reaction of γ,δ-alkenyl hydrazone **1a** and 4-chlorobromobenzene **2a** as the model substrates catalyzed by $Pd(dba)_2$/dppbz in THF at 80 °C for 24 h. The expected carboamination product **3a** was produced only in trace amount (Table 1, entry 1). We then evaluated the effect of a series of ligands (Table 1, entries 2-5), and found dppf was the most efficient in promoting this transformation, delivering **3a** in a high yield of

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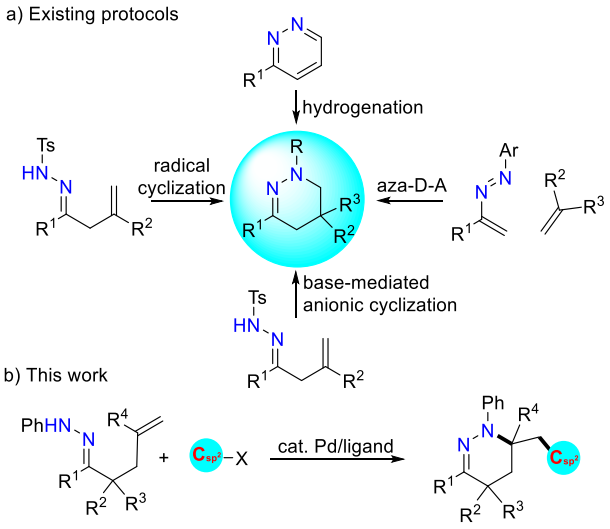
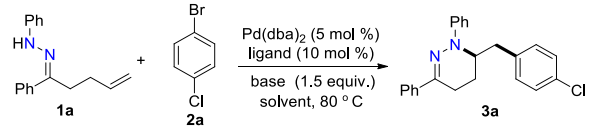


Scheme 1. Strategies for the synthesis of tetrahydropyridazines.

88%. We also noted that in the absence of ligands the yield was only 58%, indicating that some ligands can facilitate the reaction. When the reaction was performed in other solvents or with other bases (Table 1, entries 7-12), no further improvement of the yield was obtained. Finally, the conditions detailed in entry 4 was chosen as the optimal conditions.

Table 1. Optimization of the Reaction Conditions.[a)]



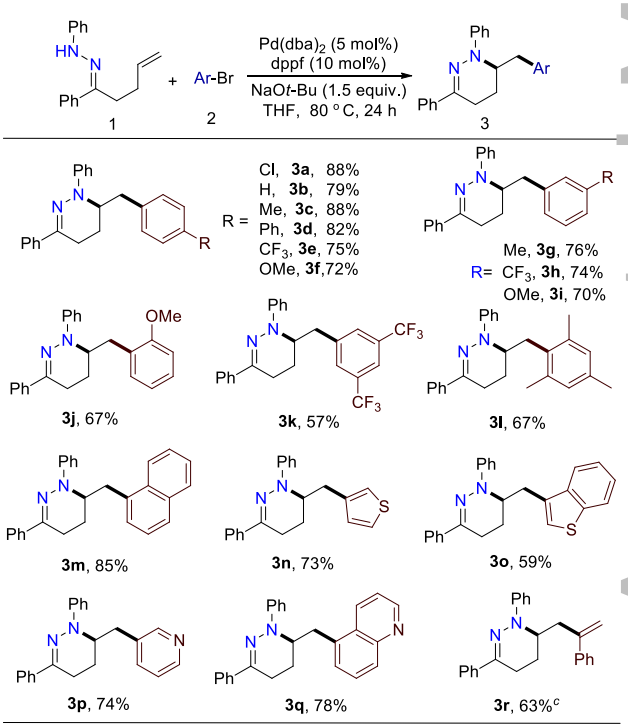
Entry	Ligand	Solvent	Base	Yield[b)]/%
1	dppbz	THF	NaO^{t}Bu	trace
2	DPEphos	THF	NaO^{t}Bu	69
3	Xantphos	THF	NaO^{t}Bu	70
4	dppf	THF	NaO^{t}Bu	88
5	PPh_3	THF	NaO^{t}Bu	56
6	----	THF	NaO^{t}Bu	58
7	dppf	toluene	NaO^{t}Bu	82
8	dppf	dioxane	NaO^{t}Bu	69
9	dppf	CH_3CN	NaO^{t}Bu	40
10	dppf	THF	K_2CO_3	trace
11	dppf	THF	CsF	26
12	dppf	THF	CH_3OK	74

[a)] Reaction conditions: hydrazone **1**a (0.20 mmol), bromobenzene **2a** (0.40 mmol, 2 equiv.), $Pd(dba)_2$ (0.01 mmol, 5 mol%), ligand (0.02 mmol, 10 mol%), base (0.30 mmol, 1.5 equiv.), solvent (2 mL), 80 °C, N_2, 24 h. [b)] Yields were estimated by NMR using CH_2Br_2 as internal reference.

With the optimized conditions in hand, we next explored the substrate scope. As shown in Table 2, the reaction of aryl bromides bearing both electron donating and electron-withdrawing substituents at the *para*-position of aryl groups proceeded smoothly to deliver the corresponding tetrahydropyridazines in good yields (**3a-3f**). The lack of obvious electronic impact indicates of the robustness of the present reaction. Similarly, various aryl bromides with electronically distinct *meta*-substitution could also be applied (**3g-3i**). Remarkably, the bulky *ortho*-substitution is also tolerated, as 2-MeO analogue **3j** was produced with a good 67% yield. Along this line, 2,4,6-trimethylphenyl (**3l**) analogue is also produced in a similar yield. Highly electron-deficient 3,5-bistrifluoromethyl bromobenzene is also competent (**3k**). Naphthyl (**3m**) and electronically distinct heterocycles (**3n-3q**) were also uneventfully installed. Besides aryl, alkenyl bromides could also be efficiently coupled. Thus, the use of α-bromostyrene delivered the expected **3r** in a good yield of 63% when PPh_3 was used as ligand in lieu of dppf.

The scope of hydrazones was next assessed under the optimized conditions. The results are summarized in Table 3. Hydrazones bearing either electron-donating or -withdrawing substituents at the aryl moiety were facilely accommodated, yielding the desired products in 56-84% yields (Table 3, **4a-4f**).

Table 2. Scope of Aryl Bromide for Pd-Catalyzed Carboamination [a,b)]



[a)] General conditions: hydrazone **1** (0.20 mmol), bromobenzene **2** (0.4 mmol, 2 equiv.), $Pd(dba)_2$ (0.01 mmol, 5 mol%), dppf (0.02 mmol, 10 mol%), NaO*t*-Bu (0.3 mmol, 1.5 equiv.), THF (2 mL), 80 °C, N_2, 24 h. [b)] Isolated yield. [c)] PPh_3 (0.02 mmol, 10 mol%) was used as a ligand.

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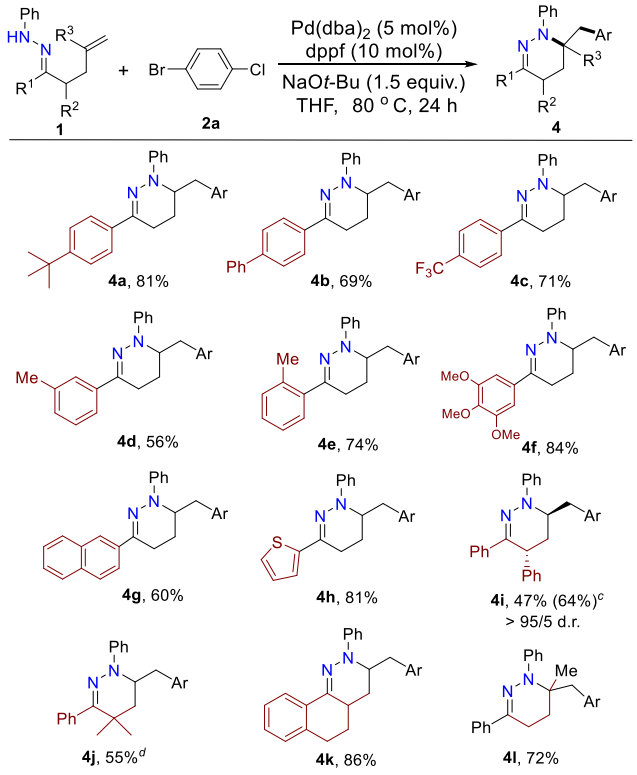
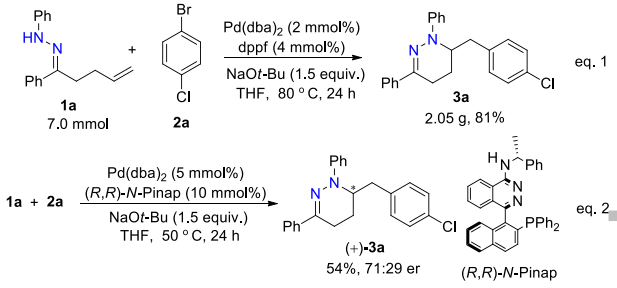
Table 3. Scope of Hydrazone for Pd-Catalyzed Carboamination [a,b]



[a] General conditions: Hydrazones **1** (0.20 mmol), bromobenzene **2** (0.4 mmol, 2 equiv.), $Pd(dba)_2$ (0.01 mmol, 5 mol%), dppf (0.02 mmol, 10 mol%), NaO*t*-Bu (0.3 mmol, 1.5 equiv.), THF (2 mL), 80 °C, N_2 atmosphere, 24 h. [b] Isolated yield. [c] PPh_3 (0.02 mmol, 10 mol%) was used as a ligand; the yield based on recovered starting material is reported in parentheses. [d] IPr (0.02 mmol, 10 mol%) was used as a ligand.

Notably, substitution at the *ortho*-position of the phenyl moiety did not jeopardize the reactivity, and **4e** was obtained in a good 74% yield. In addition, 2-naphthyl and 2-thienyl hydrazones were also tolerated, with products **4g** and **4h** being afforded in good yields (60% and 81%, respectively). The use of **1i** bearing α-phenyl delivered the expected **4i** in a moderate yield of 47% (64% yield based on recovered starting material) when PPh_3 was used as ligand in lieu of dppf. The incomplete conversion in this case may indicate of unfavourable innate substrate control exerted by the Ph group on the tether. Hydrazone **1j,** which bears α,α-dimethyl substitution at the tether, delivered the desired product **4j** in a moderate yield of 55% when NHC type ligand IPr was used as ligand. We also investigated the reaction of 1-naphthanone derived hydrazine **1k**, which also delivered the expected product **4k** in a high 86% yield. To our delight, this reaction is also capable of establishing C–N bond with a tertiary center, as tetrahydropyridazines **4l** can be facilely afforded in a good 72% yield.

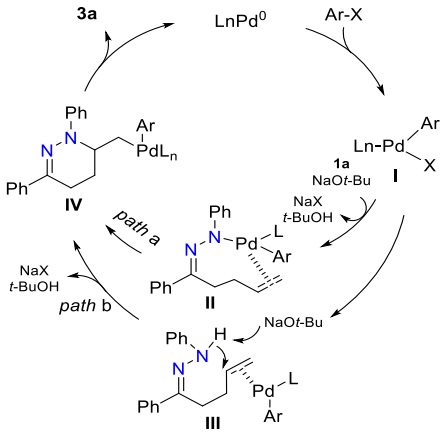
To demonstrate the practicality of this method, a gram-scale reaction was attempted. A 7 mmol scale reaction of hydrazone **1a** with 4-bromochlorobenzene **2a** catalyzed by only 2 mol% $Pd(dba)_2$ afforded 2.05 g of **3c** in only a slight drop of the yield compared to the model reaction (Scheme 2, eq. 1). Furthermore, despite the observation that the reaction can proceed without a ligand, we evaluated the effect of ligand on the possible enantio-differentiation. After some trials, it was found that the reaction of **1a** under these optimized conditions delivered product **3a** in 54% yield with 71:29 e.r. when (*R*, *R*)-*N*-Pinap was used



Scheme 2. Scale-up reaction and preliminary catalytic enantioselective synthesis.

as ligand (Scheme 2, eq 2). Further optimization is being pursued to improve the enantiocontrol.

A plausible catalytic cycle for this Pd-catalyzed carboamination reaction is shown in Scheme 3 according to literature precedents. [12f] The reaction is initiated by oxidative addition of the aryl halide to Pd(0) to afford the palladium(II) complex **I**. In an inner-sphere scenario (path a), substrate deprotonation and ligand exchange with this Pd^{II} complex produces a Pd-amido complex **II**, which then undergoes a *syn*-selective migratory insertion to provide **IV**. An outer-sphere alternative, which involves electrophilic activation of olefin by Pd(II) complex **I** and attack of the olefin by the base deprotonated hydrazone moiety (*anti*-aminopalladation), is also possible. Finally, C-C reductive elimination from complex **IV** releases the heterocyclic product **3a** and regenerates the active Pd(0) catalyst.



Scheme 3. A plausible mechanism.

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In conclusion, we have developed a facile Pd catalyzed carboamination of γ,δ-alkenyl hydrozones with various C(sp^2)-halides toward the modular assembly of various dihydroazines. Preliminary studies also showcased the feasibility of this chemistry for enantioselective synthesis. Further studies in improving the reaction efficiency and enantiocontrol are currently underway.

Experimental Section

General information

NMR spectra were recorded at 25 °C on a Varian 400, 500 or a Bruker 600 MHz spectrometer. The chemical shifts (δ) are given in parts per million (ppm) relative to internal standards (TMS, 0 ppm for ^{1}H, $CDCl_3$, 77.0 ppm for ^{13}C). High resolution mass spectra were recorded on Bruker microTOF spectrometer. Flash chromatography was performed on silica gel 60 (particle size 300-400 mesh ASTM, purchased from Taizhou, China). Copies of NMR were processed with MestReNova Software. Commercial chemicals were used as received.

General procedure for Pd-catalyzed carbamination of alkenyl hydrazones (examplified with 3a)

Under N_2 atmosphere, $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 5 mol%) and dppf (11.1 mg, 0.02 mmol, 10 mol%) were dissolved in THF (2 mL) into a 10 mL Schlenk tube. The solution was stirred at room temperature ca. 10 min, before NaO*t*-Bu (28.8 mg, 0.3 mmol, 1.5 equiv.), 1-bromo-4-chlorobenzene **2a** (76.6 mg, 0.40 mmol, 2 equiv), and hydrazone **1a** (50.1 mg, 0.20 mmol) were added sequentially. The resulting mixture was stirred at 80 ℃ for 24 h. The solution was then cooled to room temperature, the solvent removed *in vacuo* and the residue purified by column chromatography (eluent: Petroleum ether/EtOAc) to obtain **3a** (63.2 mg, 88% yield) as a yellow oil.

Acknowledgements

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UPDATE

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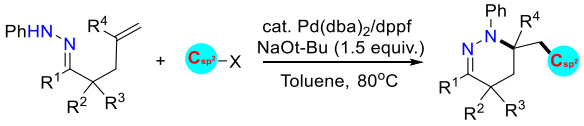

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