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Intramolecular Imidoylative Heck Reaction: Synthesis of Cyclic Ketoimines from Functionalized Isocyanide

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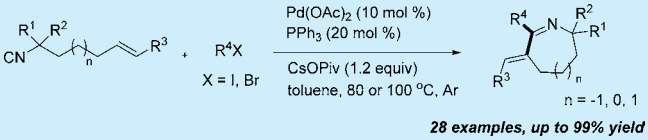
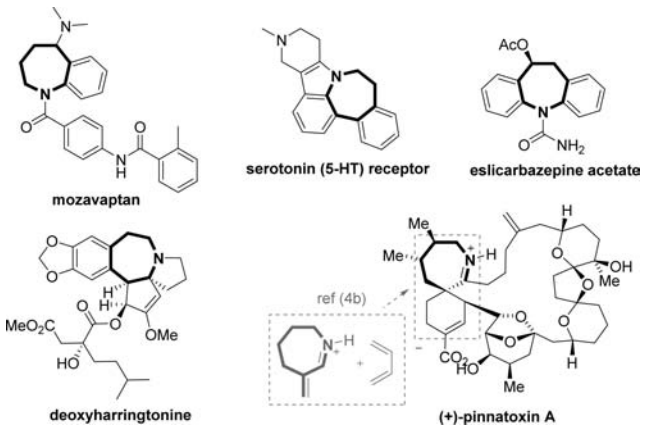
Supporting Information

ABSTRACT: Efficient access to five- to seven-membered cyclic ketoimines, through palladium-catalyzed intramolecular imidoylative Heck reaction of alkene-containing isocyanides, has been developed. Consecutive isocyanide and alkene insertion into aryl or alkyl Pd(II) intermediates takes place in this process. No byproduct derived from monoinsertion or reversed sequence is detected.



Azepines, a class of seven-membered *N*-heterocycles, are ubiquitous in many bioactive synthetic compounds as well as natural products (Scheme 1). For example, mozavaptan is a drug used in Japan for the treatment of paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone.[1] Eslicarbazepine acetate is an efficient drug used for the treatment of adjunctive therapy for partial onset of seizures.[2] Deoxyharringtonine, isolated from the *Cephalotaxus* genus, is an important antileukemia alkaloid exhibiting acute toxicity toward P388 and L1210 leukemia cells.[3] Spiroimine-containing alkaloid (+)-pinnatoxin A is a toxic amphoteric macrocycle isolated from the Okinawan bivalve *Pinna muricata*.[4a] Traditional preparation of such azepine derivatives was mainly based on ring-expansion reactions,[5a] Beckman rearrangements,[5b] and other multistep sequences.[5c,d] However, a general and efficient method for the construction of azepine derivatives remains an attractive synthetic task.[6]

Scheme 1. Representative Molecules Containing the Azepine Moiety



In recent years, nonfunctionalized isocyanides have been extensively studied in palladium-catalyzed imidoylation reactions to synthesize acyclic imine derivatives.[7,8] To access to cyclic products using nonfunctionalized isocyanides, a nucleophilic group is usually preinstalled in a precursor of imidoyl Pd(II) intermediate, formed either from oxidative addition or C−H bond activation followed by isocyanide insertion.[9] For example, 4-aminoquinazolines were efficiently accessed from *N*-(2-bromoaryl)amidines[9a] or *N*-arylamidines[9b] through palladium-catalyzed imidoylative cyclization and tautomerization, developed by Maes and our group, respectively. Besides, cyclic guanidine and related heterocycles could be synthesized by Pd-catalyzed oxidative imidoylative coupling using substrates containing two nucleophilic heteroatoms.[10] In these nonfunctionalized isocyanide approaches, isocyanide is used as a C1 synthon, and only the terminal carbon of isocyanide is contributed to the ring construction. On the other hand, by using the so-called functionalized isocyanide strategy, multiple atoms including the isocyanide nitrogen could be introduced to the ring.[11] Therefore, the diversity of isocyanide could be fully used, demonstrating the advantage of isocyanide over carbon monoxide CO in relevant carbonylation reactions. By applying this approach, indole derivatives,[11a,b] camptothecin analogues,[11c] multisubstituted oxazoles,[12] and phenanthridines[13] were efficiently prepared (Scheme 2).

Concerning the size of the rings formed, the synthesis of seven-membered *N*-heterocycles through Pd-catalyzed imidoylation of functionalized isocyanide was unprecedented (Scheme 2). Herein, we developed efficient access to seven-membered cyclic ketoimines starting from alkene-containing isocyanides. In this imidoylative Heck process, isocyanide and alkene underwent insertion to Pd(II) intermediate sequentially, affording 6-methylene-3,4,5,6-tetrahydro-2*H*-azepines exclusively. In addition, by altering the length between the isocyano

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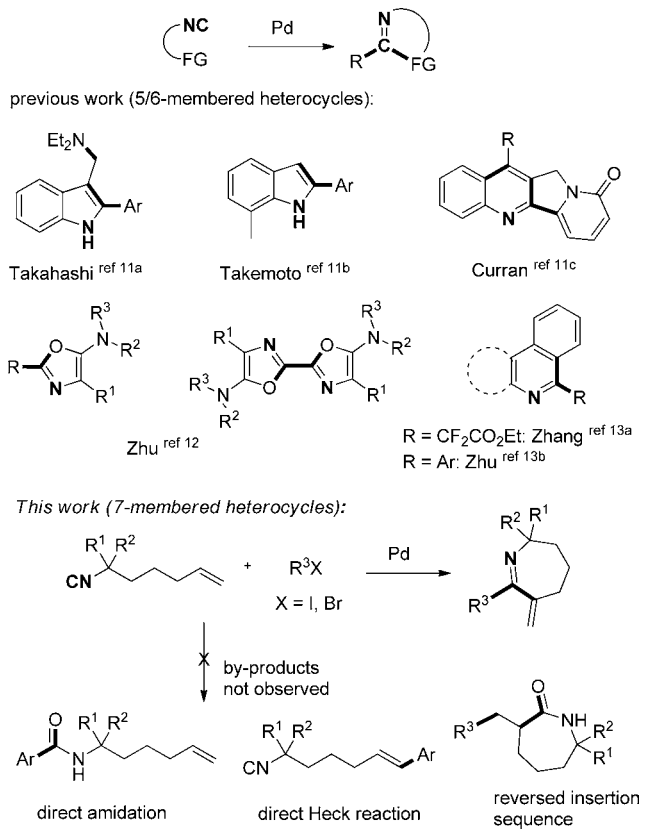
Scheme 2. Pd-Catalyzed Functionalized Isocyanide Strategy for the Synthesis of *N*-Heterocycles

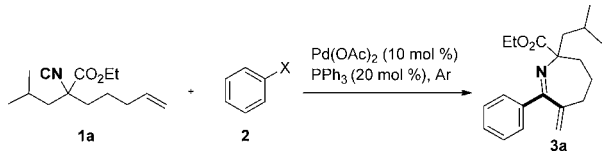


and alkenyl moieties, five- and six-membered cyclic imines could also be obtained.

The reaction conditions were screened with ethyl 2-isobutyl-2-isocyanohept-6-enoate **1a** and iodobenzene as model substrates. However, a reaction of premixed reactants under normal Heck conditions ($Pd(OAc)_2$, PPh_3, Na_2CO_3 in toluene) yielded only a messy mixture. When a solution of isocyanide **1a** in toluene was introduced to the reaction mixture slowly, the desired product, ethyl 2-isobutyl-6-methylene-7-phenyl-3,4,5,6-tetrahydro-2*H*-azepine-2-carboxylate **3a**, was formed in 18% NMR yield (entry 1, Table 1). Screening of bases revealed that CsOPiv was the base of choice for this imidoylative Heck reaction, and **3a** could be obtained in 70% yield (entries 2−5). The reaction was equally efficient in DMSO, but less efficient in dioxane or CH_3CN (entries 6−8). The yield of **3a** was increased to 81% when a solution of **1a** in 1 mL of toluene was added via a syringe pump during 1 h (entry 9). The yield decreased to 45% at 70 °C (entry 10) and 56% with 5 mol % of $Pd(OAc)_2$ and 10 mol % of PPh_3 (entry 11). When using bromobenzene as the arylating reagent, the same product **3a** was generated in 85% yield at elevated temperature (100 °C, entry 12). (For more details, see Supporting Information.)

With the optimized conditions in hand, the substrate scope of electrophiles was investigated first (Scheme 3). Substituents such as OMe, Ph, Cl, Br, CO_2Me, COMe, CN, NO_2, and CHO on aryl iodide were well tolerated in reactions with ethyl 2-isobutyl-2-isocyanohept-6-enoate **1a**, generating the corresponding products in good to excellent yields (**3a**−**l**). When 1-chloro-2-iodobenzene was used as the substrate, the reaction was messy and a only trace product was detected by LC−MS, indicating that the reaction was sensitive to steric hindrance.

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base (1.2 equiv)	temp (°C)	yield[b] (%)
1[c]	toluene	Na_2CO_3	80	18
2[c]	toluene	K_2CO_3	80	18
3[c]	toluene	Cs_2CO_3	80	30
4[c]	toluene	CsOPiv	80	70
5[c]	toluene	Et_3N	80	25
6[c]	DMSO	CsOPiv	80	70
7[c]	dioxane	CsOPiv	80	33
8[c]	CH_3CN	CsOPiv	80	40
9[c,e]	toluene	CsOPiv	80	81 (79)[f]
10[c,g]	toluene	CsOPiv	80	56[f]
11[c]	toluene	CsOPiv	70	45[f]
12[d,e]	toluene	CsOPiv	100	85 (82)[f]

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), PPh_3 (0.04 mmol, 20 mol %), base (0.24 mmol), Ar. A solution of **1a** in solvent (1 mL) was added slowly within 1 h. [b]NMR yield with 1-iodo-4-methoxybenzene as an internal standard. [c]X = I. [d]X = Br. [e]A solution of **1a** in toluene (1 mL) was added via a syringe pump within 1 h. [f]Isolated yield. [g]5 mol % of $Pd(OAc)_2$ and 10 mol % of PPh_3.

Azepines **3a** and **3d** were also accessed in 82% and 92% yields, respectively, using corresponding aryl bromides at 100 °C. Sterically hindered 1-iodonaphthalene afforded the product **3m** in lower yield (59%). Heteroaryl halides could also participate in the reaction smoothly, generating **3n**−**q** in comparable yields. A symmetrical bis-azepine **3r** was obtained in 76% yield using 1,4-diiodobenzene as the coupling partner. When *N*-(2-iodophenyl)-*N*-methylmethacrylamide was applied in the reaction, a cascade process involving alkene, isocyanide, and alkene insertion took place sequentially to give a methylene-tethered oxindole−azepine pair **3s** in 61% yield. When alkenyl and alkynyl bromides were carried out in the reaction, no corresponding products were generated. It is notable that gram-scale preparation of **3f** (1.37 g) was accessible in 70% yield.

Then, the scope of isocyanide was studied in reactions with iodobenzene under the standard conditions (Scheme 4). Other α-alkylated methyl 2-isocyanohept-6-enoates were tested, and the corresponding azepines (**4a**−**c**) were obtained in excellent yields. Substrate containing two alkenyl groups reacted smoothly to give **4d**, with the other alkenyl group unreacted, in 83% yield. Other electron-withdrawing groups such as phosphate were well tolerated in the reaction (**4e**). In addition to azepines, six- and five-membered cyclic imines were obtained as well by shortening the alkenyl carbon chain (**4f,g**). It is worth of mentioning that α-unsubstituted ethyl 2-isocyanopent-4-enoate also survived the reaction, generating 4-methylene-3,4-dihydro-2*H*-pyrrole derivative **4h** in 72% yield. Internal alkene underwent the insertion reaction smoothly, generating trisubstituted exocyclic alkene **4i** in 97% yield. Unfortunately, eight-membered and larger sized cyclic imines could not be synthesized by extending the distance between the isocyano and alkenyl groups under the same reaction conditions.

Similar to the reported imidoylation reactions, the current imidoylative Heck reaction is likely initiated by oxidative addition of aryl halide to Pd(0), as shown in Scheme 5.[5]

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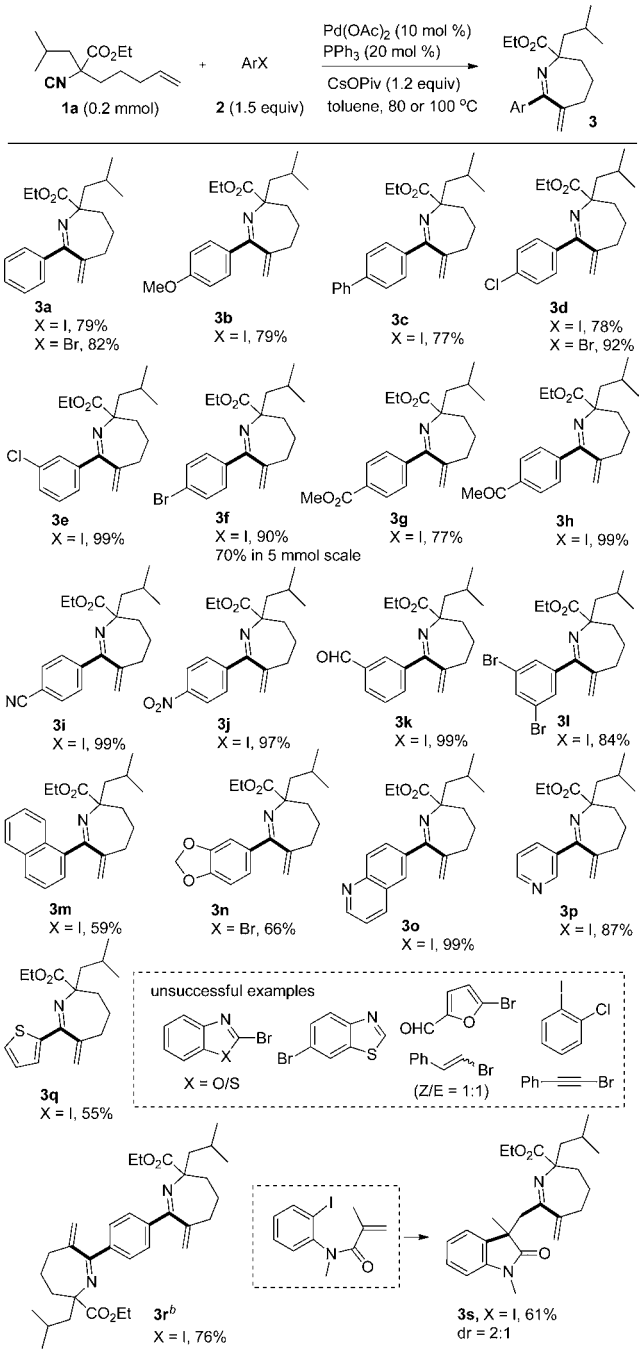
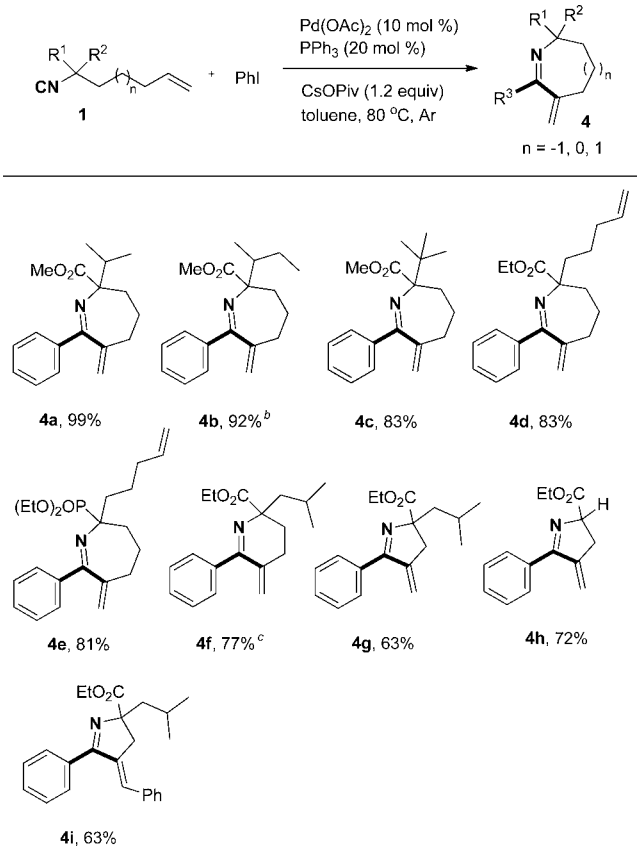
Scheme 3. Substrate Scope of Aryl Halides[a]



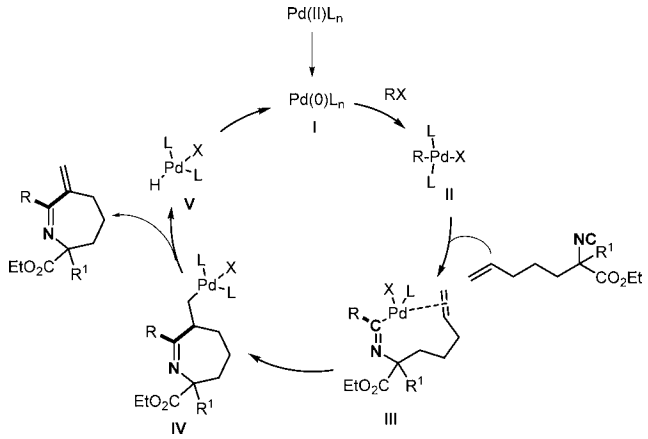
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), PPh_3 (0.04 mmol, 20 mol %), CsOPiv (0.24 mmol), 80 °C (X = I) or 100 °C (X = Br), Ar. **1a** in toluene (1 mL) was added to the reaction mixture (in 1 mL of toluene) via a syringe pump within 1 h. Isolated yields were given. [b]**1a** (0.2 mmol), 1,4-diiodobenzene (0.1 mmol).

Scheme 4. Substrate Scope of Isocyanides[a]



[a]Reaction conditions: **1** (0.2 mmol), PhI (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), PPh_3 (0.04 mmol, 20 mol %), CsOPiv (0.24 mmol), 80 °C, Ar. A solution of **1** in toluene (1 mL) was added to the reaction mixture via a syringe pump within 1 h. Isolated yields were given. [b]dr = 2.6:1. [c]THF as solvent.

Scheme 5. Proposed Mechanism



Migratory isocyanide insertion to intermediate **II** affords imidoyl Pd(II) intermediate **III**. The following intramolecular alkene insertion and β-hydride elimination via **IV** yields the final product and regenerates Pd(0) to complete the catalytic cycle.

In conclusion, we have developed an efficient and practical method for the synthesis of imine-containing azepines via palladium-catalyzed imidoylative Heck reaction. Seven-membered heterocycles were first synthesized using the functionalized isocyanide under palladium catalysis. The reaction proceeds through consecutive isocyanide and alkene insertion into aryl or alkyl Pd(II) intermediates, and no byproduct derived from monoinsertion or reversed sequence is detected. A broad range of substrates are applicable to the reaction in good to excellent yields. These five- to seven-membered cyclic imine products bearing an exocyclic methylene group may serve

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as useful building blocks in the synthesis of more complicated *N*-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01174.

General experimental procedures and characterization data of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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