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Palladium-Catalyzed Intramolecular Insertion of Alkenes into the Carbon−Nitrogen Bond of β-Lactams

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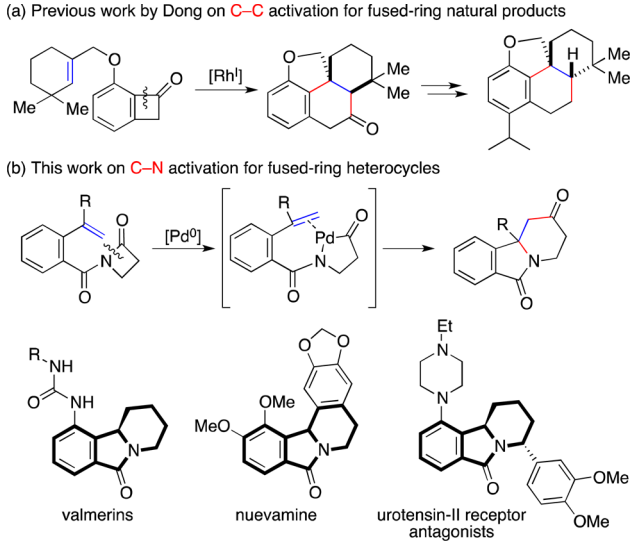
Supporting Information

ABSTRACT: The carbon−nitrogen bond of β-lactams is cleaved by palladium(0), and an alkene is intramolecularly inserted therein. The following reductive elimination produces nitrogen-containing benzo-fused tricycles in good to high yields.

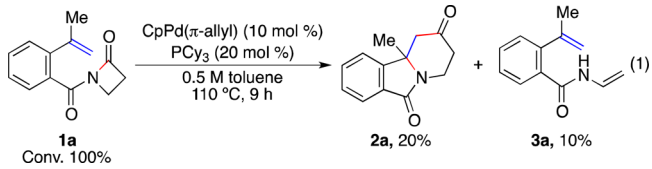
Transition-metal-catalyzed activation of unreactive nonpolar carbon−carbon[1] and carbon−hydrogen[2] σ bonds has demonstrated its applicability to various synthetic transformations in the past decades. In particular, insertion of unsaturated functionalities into a C−C σ bond of cyclic compounds offers an atom- and step-economical method to construct ring-expanded products (Scheme 1a).[3] This strategy, recently coined as the "cut-and-sew" protocol,[3c] is especially viable in intramolecular cases. It presents access to fused-ring compounds that are synthetically important building blocks and/or structural frameworks found in myriads of natural products (Scheme 1a).[4]

Scheme 1. Transition-Metal-Catalyzed Alkene Insertion into Unreactive σ Bonds



Building on the C−C bond cleavage chemistry, we envisaged that transition-metal-catalyzed activation of a carbon−nitrogen σ bond of cyclic compounds followed by alkene insertion might serve as the key step to furnish nitrogen-containing fused heterocycles. Successful examples of alkene insertion into cyclobutanone[5] led us to study structurally related β-lactams as potential-rich and readily accessible substrates for such a purpose.[6] In general, the lone-pair electrons of the nitrogen atom of an amide linkage are delocalized onto the carbonyl group, rendering the C−N bond stronger. However, the double-bond character of the C−N bond of a β-lactam is reduced as a result of the angle strain of the four-membered ring.[6i,7,8] Although various methods to activate C−N σ bonds with transition metals have been developed,[9] there have been no reports on the cleavage of the carbonyl C−N bond of β-lactams by transition metals leading to the "cut-and-sew" approach.[10] Herein we report a palladium-catalyzed intramolecular insertion of alkenes into carbonyl C−N bonds of β-lactams to afford nitrogen-containing tricycles, benzoindolizinediones (Scheme 1b), which are key motifs in many pharmaceuticals and natural products, such as valmerins,[11] nuevamine,[12] and urotensin-II receptor antagonists.[13]

In order to test the proposed strategy, β-lactam **1a** was employed as the model substrate, and a variety of ligands for palladium(0) were examined. The initial survey of ligands revealed that electron-rich and bulky PCy_3 afforded the desired benzoindolizinedione **2a** in ca. 20% yield along with vinyl amide **3a** (ca. 10%) (eq 1).



A plausible reaction mechanism is illustrated in Scheme 2. The carbonyl C−N bond of the substrate **1** oxidatively adds to palladium(0) to form the five-membered palladacycle **A**. Subsequent intramolecular insertion of the alkene moiety into the Pd−N bond[14] forms the seven-membered palladacycle **B**. The following reductive elimination furnishes **2** and palladium(0). Another mechanistic pathway forming the ring-opened vinyl amide **3** branches off after the first step. Decarbonylation from **A** generates the four-membered palladacycle **C**, and β-hydride elimination followed by reductive elimination affords **3** and regenerates palladium(0).

To improve the yield of **2a** as well as the selectivity (**2a**/**3a**), a variety of parameters such as ligands, Pd precatalysts, solvents, temperature, and concentration were then examined. The selected optimization studies are summarized in Table 1.[15] A

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Scheme 2. Plausible Reaction Mechanism

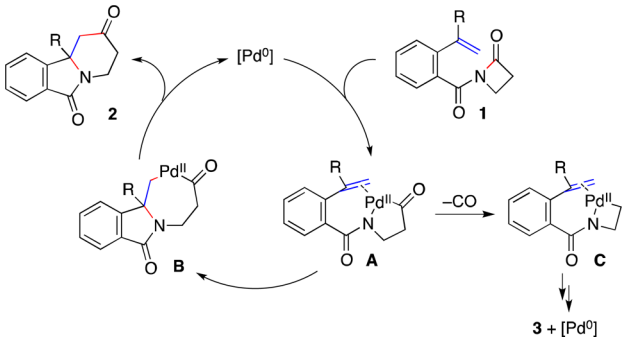
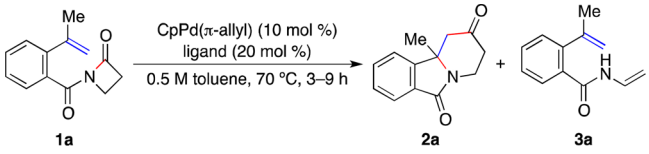
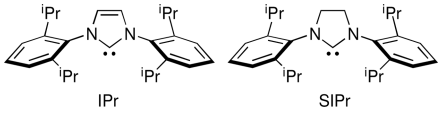


Table 1. Selected Optimization Studies[a]



		yield (%)[b]	
entry	ligand	2a	3a
1	PCy_3	35	3
2	PMe_3	4	0
3	P^tBu_3	0	39
4	IPr	31	0
5	SIPr	81	0
6[c]	SIPr	93 (91[d])	0

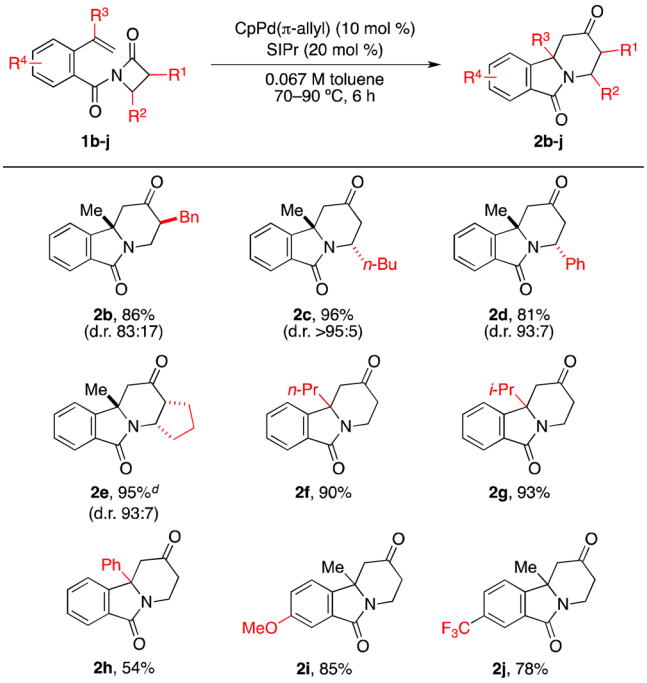
[a]**1a** (0.10 mmol), CpPd(π-allyl) (10 mol %), ligand (20 mol %), toluene, 70 °C. [b]NMR yields. [c]Run at 0.10 M. [d]0.50 mmol scale. Isolated yield.



lower reaction temperature (70 °C) slightly improved the product selectivity (**2a**, 35%; **3a**, 3%) (entry 1). Other trialkylphosphine ligands such as PMe_3 and P^tBu_3 were not as effective as PCy_3 (entries 2 and 3). In contrast, N-heterocyclic carbene (NHC) ligands, which are more electron-donating than phosphine ligands, gave better results. 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), for instance, suppressed the formation of **3a**, although almost the same level of production of **2a** was observed (entry 4). To our delight, the use of 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene (SIPr), the saturated analogue of IPr, significantly improved the yield of **2a** to 81% (entry 5). Although SIPr is regarded to have a similar electron-donating ability as IPr,[16] the conformational flexibility induced by saturation of the backbone might be beneficial for the present reaction.[17] Finally, dilution of the reaction system improved the yield to 93% (entry 6).[18]

Various β-lactams **1** were then subjected to the ring-expansion reaction under the optimized reaction conditions (Table 2). Those bearing alkyl and aryl substituents at the 3- and 4-positions successfully participated in the reaction, giving the desired benzoindolizinediones in good to excellent yields with diastereoselectivities ranging from 83:17 to >95:5 (**2b–d**). The reaction of a β-lactam containing a cyclopentane ring (**1e**) also proceeded well with 5 mol % palladium catalyst, though the reaction required a prolonged reaction time (21 h).

Table 2. Substrate Scope of Palladium-Catalyzed Reaction of 1[a,b,c]



[a]**1** (0.10 mmol), CpPd(π-allyl) (10 mol %), SIPr (20 mol %), toluene, 70 °C (for **1b** and **1h–j**) or 90 °C (**1c–g**). [b]Isolated yields are shown. [c]The major diastereomer is depicted. Diastereomeric ratios (d.r.) determined by ^1H NMR analysis of the crude reaction mixture are shown. [d]Run with CpPd(π-allyl) (5 mol %) and SIPr (10 mol %) for 21 h.

The diastereoselectivity observed with **2b** may be ascribed to the formation of the thermodynamically favored conformation in which a benzyl substituent (R^1) occupies an equatorial position. On the other hand, the diastereoselectivities observed with products **2c–e** can be ascribed to the alkene insertion step (**A** to **B** in Scheme 2), where the alkene coordinates to the palladium center in a way that avoids the steric repulsion between the methyl group on the alkene and the β-lactam substituents (R^2) (Figure 1). The substituents on the inserting

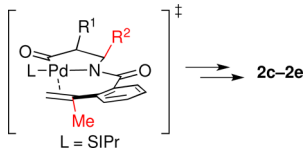


Figure 1. Plausible transition state for alkene insertion.

alkene were also examined. Both propyl-substituted and isopropyl-substituted alkenes inserted well (**2f** and **2g**), whereas the phenyl-substituted alkene led to a diminished yield of 54% (**2h**). The attempted reactions of β-lactams bearing a nonsubstituted vinyl group, monosubstituted vinyl group, or 1,2-disubstituted vinyl group (**4–6** in Figure 2) were futile even at elevated temperature.[19] Methoxy and trifluoromethyl substituents on the tethered benzene ring were also tolerated, affording the desired tricyclic products in good yields (**2i** and **2j**). Although we also examined the reaction of substrate **7** having an aliphatic chain as the tether, the desired indolizinedione was not observed.[20]

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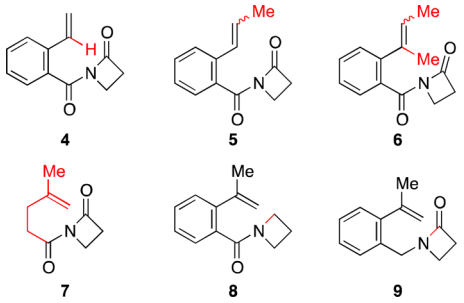
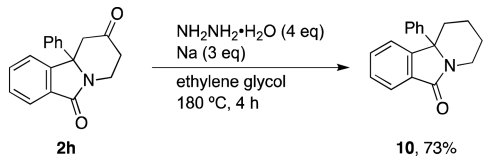


Figure 2. Other attempted β-lactams.

Since many biologically active compounds and natural products contain the indolizidinone skeleton, the deoxygenated analogue of indolizinedione, the carbonyl group of the product was converted into a methylene group (eq 2). Thus, treatment



(2)

of **2h** with hydrazine and sodium in refluxing ethylene glycol[11] allowed selective deoxygenation of the keto carbonyl group, giving a 73% yield of **10**, which is known as a non-nucleoside HIV-1 reverse transcriptase inhibitor.[21]

Next, the significance of the ring carbonyl and tether carbonyl groups was examined. At the outset of the project, the seminal work reported by Matsubara and Kurahashi on the nickel-catalyzed decarbonylative alkyne insertion reaction of phthalimides[9f,g] led us to use imide-like β-lactams. In order to observe the effect of the two carbonyl groups, substrates **8** lacking the ring carbonyl group and **9** lacking the tether carbonyl group were synthesized (Figure 2). Both substrates were treated under the same reaction conditions as before but yielded no desired products even at elevated temperature. These experiments showed that the presence of the both carbonyl groups is requisite for the reactivity. We assume that the tether carbonyl group also accepts electron density from the nitrogen to further weaken the double-bond character between the nitrogen and the ring carbonyl carbon.

In summary, we have developed a reaction involving intramolecular alkene insertion into the carbonyl C−N bond of β-lactams to access tricyclic nitrogen heterocycles. This implies the possibility of activation of other carbon−heteroatom σ bonds and insertion of unsaturated functionalities therein, resulting in the construction of fused-ring heterocyclic systems. An asymmetric version and other heteroatom variants of this reaction are currently being investigated in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05308.

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Notes

The authors declare no competing financial interest.

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(18) We synthesized the saturated analogue of **1a** and reacted it under the optimized conditions, which resulted in recovery of the starting material without the observation of any byproduct derived from decarbonylation. This demonstrates that the alkene moiety also serves as a directing group for oxidative addition of the C−N bond of the β-lactam.
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