Heterocycles

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Palladium-Catalyzed Oxidative Carbonylation of *N*-Allylamines for the Synthesis of β-Lactams**

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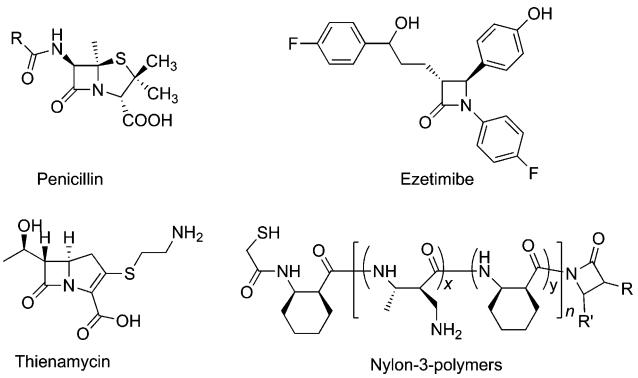
Abstract: *β-Lactam scaffolds are considered to be ideal building blocks for the synthesis of nitrogen-containing compounds. A new palladium-catalyzed oxidative carbonylation of N-allylamines for the synthesis of α-methylene-β-lactams is reported. DFT calculations suggest that the formation of β-lactams via a four-membered-ring transition state is favorable.*

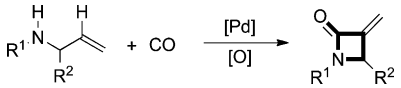
As one of the most important heterocyclic compounds, β-lactams have been considered a privileged structure in chemical, pharmaceutical, and materials industries.[1] Moreover, the β-lactam scaffold is considered an ideal building block for the synthesis of nitrogen-containing compounds which widely exist in vitamins, alkaloids, antibiotics, etc. For example, the core structures of penicillin antibiotics, thienamycin antibiotics, and ezetimibe,[2] are β-lactams (Scheme 1). This four-membered ring has also been used as a synthon in the preparation of various non-β-lactam compounds of biological significance.[3] For example, nylon 3 polymers are synthesized from β-lactams through ring-opening polymerization.[4]

Among the synthetic methods to obtain β-lactams, the Staudinger synthesis, the formal [2+2] cycloaddition of imines to ketenes, is well known.[5] However, generation of the ketene requires treatment of activated carboxylic acid derivatives such as acyl chlorides which sometimes limits its potential. Considering the large pharmacological importance of β-lactams, the search for simple, efficient, and economic methods, as well as control of the stereoselectivity and regioselectivity, has attracted the attention of synthetic chemists, but great challenges still remain.



Scheme 1. Examples of important β-lactam-containing pharmaceuticals and β-lactam units.

Carbonylation of organic compounds with CO is an effective approach for introducing a carbonyl group into organic molecules, and has attracted much attention from synthetic chemists in the past two decades.[6] Several approaches for the synthesis of β-lactams by palladium-catalyzed carbonylation have been reported. However, these methods generally require multistep procedures, not-readily-available starting materials, and substrate pre-functionalization, such as organobromides or aziridines.[7] Oxidative carbonylation of simple nucleophiles such as C–H or Y–H (Y = O, N, etc), has been considered as an ideal carbonylation approach in recent years.[8] However, to the best of our knowledge, no example has been reported on the oxidative *N*-allylamine carbonylation for the direct synthesis of β-lactams. Herein, we communicate the first report on a practical synthesis of β-lactams by palladium-catalyzed oxidative carbonylation of *N*-allylamines (Scheme 2).



Scheme 2. Oxidative carbonylation for β-lactam synthesis.

For the initial model reaction, we selected *N*-allyl-4-methylaniline (**1a**) as the substrate. After considerable optimization, 1 atmoshpere of CO in the presence of $PdCl_2$ (10 mol%), PCy_3 (20 mol%), $Cu(OAc)_2$ (2.0 equiv), and PivOH (2.0 equiv) in DMF at 100 °C for 1 hour afforded the desired product **2a** in 71% yield (Table 1, entry 1). The

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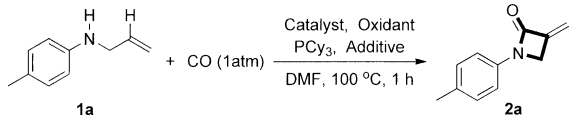
Table 1: Carbonylation of *N*-allyl-4-methylaniline.[a]



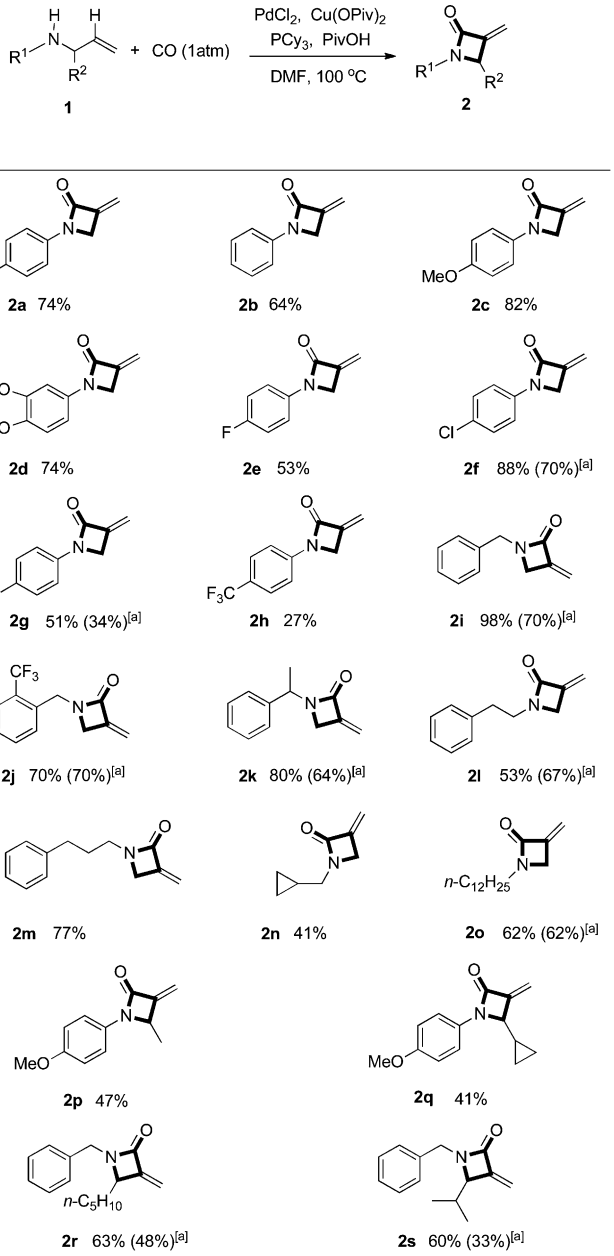
1a 2a

Entry	Catalyst	Oxidant	Additive	Yield [%][b]
1	$PdCl_2$	$Cu(OAc)_2$	PivOH	71
2	$[PdCl_2(PPh_3)_2]$	$Cu(OAc)_2$	PivOH	62
3	$[Pd(dba)_2]$	$Cu(OAc)_2$	PivOH	12
4	$PdCl_2$	$Cu(OAc)_2$	PivOH	54[c]
5	$PdCl_2$	$Cu(OAc)_2$	HOAc	56
6	$PdCl_2$	$Cu(OPiv)_2$	PivOH	74 (74)[d]
7	$PdCl_2$	$Cu(OPiv)_2$	–	53
8	$PdCl_2$	–	PivOH	0
9	–	$Cu(OPiv)_2$	PivOH	0

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (0.02 mmol), PCy_3 (0.04 mmol), oxidant (0.4 mmol), additive (0.4 mmol), and solvent (2 mL) under 1 atm of CO at 100 °C for 1 h. [b] Yields were determined by gas chromatography (GC) using biphenyl as an internal standard. [c] 80 °C. [d] Yield of isolated product. dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, Piv = pivaloyl.

structure of **2c** was confirmed by $^1H/^{13}C$ NMR spectroscopy, high-resolution mass spectrometry (HRMS), and X-ray crystal diffraction analysis (see the Supporting Information). Other palladium catalysts, such as $[PdCl_2(PPh_3)_2]$ and $[Pd(dba)_2]$, were less effective and afforded **2a** in yields of 62% and 12%, respectively. When the reaction was carried out at a lower reaction temperature, the yield decreased to 54% (Table 1, entry 4). The yield of the desired product decreased when HOAc was used as an additive (Table 1, entry 5). Actually, under the reaction conditions used in entry 1 of Table 1, the *N*-acetylation product was observed as a side product and the acetyl group was believed to be generated from $Cu(OAc)_2$. Therefore, $Cu(OPiv)_2$ was used to replace $Cu(OAc)_2$ as the oxidant (Table 1, entry 6), thus completely inhibiting the acylation and increasing the yield of the product to 74%. In the absence of acid, we only obtained a moderate yield of the desired product (Table 1, entry 7). It was also notable that no product was observed in the absence of $Cu(OPiv)_2$ or $PdCl_2$ (Table 1, entries 8 and 9). After a brief screen of the reaction conditions we found the optimized reaction required treatment of **1a** with $PdCl_2$ (10 mol%), PCy_3 (20 mol%), $Cu(OPiv)_2$ (2.0 equiv), and PivOH (2.0 equiv) under 1 atmosphere of CO with DMF as the solvent at 100 °C for 1 hour (Table 1, entry 6).

Encouraged by these initial results, we next evaluated the substrate scope of this reaction (Scheme 3). Various *N*-allylamines such as *N*-allylanilines, *N*-allylbenzylamines, *N*-allyl-alkylamines, and branched *N*-allylamines were tested. We firstly investigated the linear *N*-allylamines in which on the phenyl ring had electron-donating substituents, such as methyl and methoxy groups, and the carbonylation reaction proceeded in high efficiency (**2a**, **2c**, and **2d**). Electron-deficient *N*-allylanilines, for example, *N*-allyl-4-(trifluoromethyl)aniline, was not a good substrate for this reaction, thus giving a decreased yield of 27% after 24 hours (**2h**). Interestingly, *N*-allyl-4-chloroaniline underwent the carbonylation reaction with a yield of 88% (**2f**). Various substituents

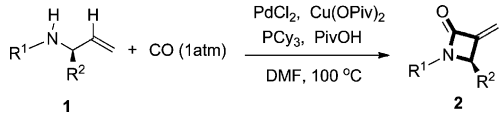


Scheme 3. Carbonylation of various *N*-allylanilines to give α-methylene-β-lactams. Reaction conditions: 100 °C, *N*-allylamine (0.2 mmol), $PdCl_2$ (10 mol%), PCy_3 (20 mol%), $Cu(OPiv)_2$ (0.4 mmol), PivOH (0.4 mmol), CO (1 atm), DMF (2 mL), 1–24 h. Yield of isolated **2** is given. [a] The reactions were carried out in an autoclave.

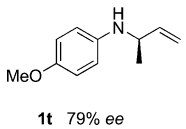
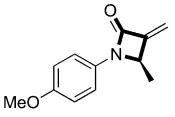
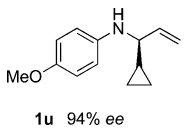
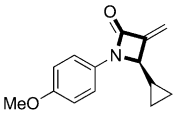
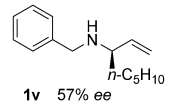
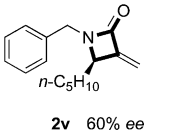
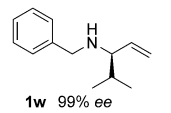
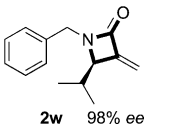
such as F, Cl, and Br were also found to be compatible (**2e**–**g**), thus suggesting the potential for further functionalization. *N*-allyl benzylamines, *N*-allyl phenethylamine, and *N*-(3-*p*henylpropyl)prop-2-en-1-amine exhibited higher reactivity, although in some cases only moderate yields were obtained (**2i**–**m**). To our delight, a cyclopropyl substituent was well tolerated in this reaction (**2n** and **2q**). A long-chain *N*-allylamine successfully provided the corresponding carbonylated product **2o** in 62% yield, and the branched *N*-allylamines surveyed under these reaction conditions led to the corresponding products (**2p**, **2r**, and **2s**) in moderate yields.

To further investigate the reaction of β-lactams generated by palladium-catalyzed oxidative carbonylation of *N*-allylamines, the subsequent study was focused on the enantioenriched *N*-allylamines. To our delight, enantioenriched *N*-allylamines could be readily transformed into their corresponding β-lactam derivatives without loss of enantioselectivity under the standard reaction conditions (Table 2). Synthesis of optically pure α-methylene-β-lactam scaffolds provides a useful platform for the synthesis of various biologically interesting β-lactam derivatives.

Table 2: Carbonylation of various enantioenriched *N*-allylamines to give α-methylene-β-lactams.[a]

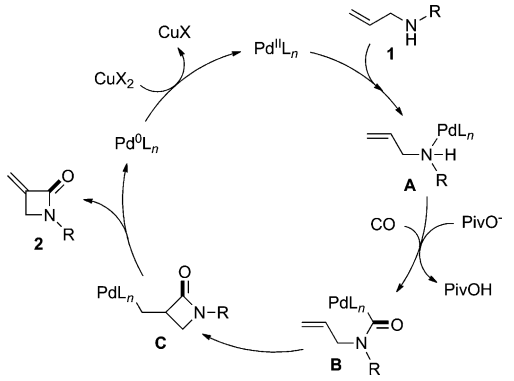


1 **2**

Entry	Substrate	Product	*t* [h]	Yield [%][b]
1	 **1t** 79% *ee*	 **2t** 78% *ee*	19	36
2	 **1u** 94% *ee*	 **2u** 93% *ee*	21	41
3	 **1v** 57% *ee*	 **2v** 60% *ee*	5	60
4	 **1w** 99% *ee*	 **2w** 98% *ee*	5	54

[a] Reaction conditions: 100 °C, *N*-allylamine (0.2 mmol), $PdCl_2$ (10 mol%), PCy_3 (20 mol%), $Cu(OPiv)_2$ (0.4 mmol), PivOH (0.4 mmol), CO (1 atm), DMF (2 mL). [b] Yield of isolated product. The *ee* values were determined by HPLC using a ciral column.

A possible mechanism for this reaction has been outlined in Scheme 4. The intermediate **A** is formed by the chelation of **1** to palladium, and subsequent migratory insertion of the coordinated CO into the nitrogen–palladium bond forms **B**.[9] The key results for the pathways leading to β-lactams are illustrated in Scheme 5. The calculated free energy of forming species **I** from 1-TS is 26.6 kcal mol^{-1}. It undergoes β-hydride elimination via transition-state 2-TS with an activation free energy of 19.9 kcal mol^{-1}. This result is in agreement with the experimental data for **2b**. In contrast, the calculated activation free energy for the formation of the five-membered product via transition-state 3-TS is 33.5 kcal mol^{-1}, and undergoes β-hydride elimination through transition-state 4-TS with an activation free energy of 6.2 kcal mol^{-1}, thus suggesting that thermodynamic control resulting in **3b** is, in this case undesirable.



Scheme 4. A possible mechanism for carbonylation.

In summary, we have developed a highly selective and practical method for the synthesis of α-methylene-β-lactams. Notably, this transformation offers a general, simple, efficient, and environmentally benign process for converting readily available *N*-allylamines directly into potentially useful compounds in the presence of CO. Moreover, various functional groups were well tolerated under the optimized reaction conditions. Preliminary mechanistic studies suggest that the formation of β-lactams via a four-membered-ring transition state is favorable. This approach has the potential to be used in many different areas of organic and medicinal chemistry, and could possibly be applied in the chemical and pharmaceutical industries.

Experimental Section

General procedure for the palladium-catalyzed carbonylation of *N*-allylamines: A balloon filled with CO was connected to an oven-dried Schlenk tube equipped with a stir bar, $PdCl_2$ (0.02 mmol), $Cu(OPiv)_2$ (0.4 mmol), and PCy_3 (0.04 mmol), PivOH (0.4 mmol), and the tube was purged five times. DMF (2.0 mL) was then added to reaction mixture by syringe, and the *N*-allylamine (0.2 mmol) was introduced. The Schlenk tube was heated at 100 °C for 1–24 h (as monitored by TLC) and then cooled to room temperature. After the gas in the balloon was released carefully, the reaction was quenched with a saturated potassium carbonate solution and extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel using petroleum ether and ethyl acetate (5:1).

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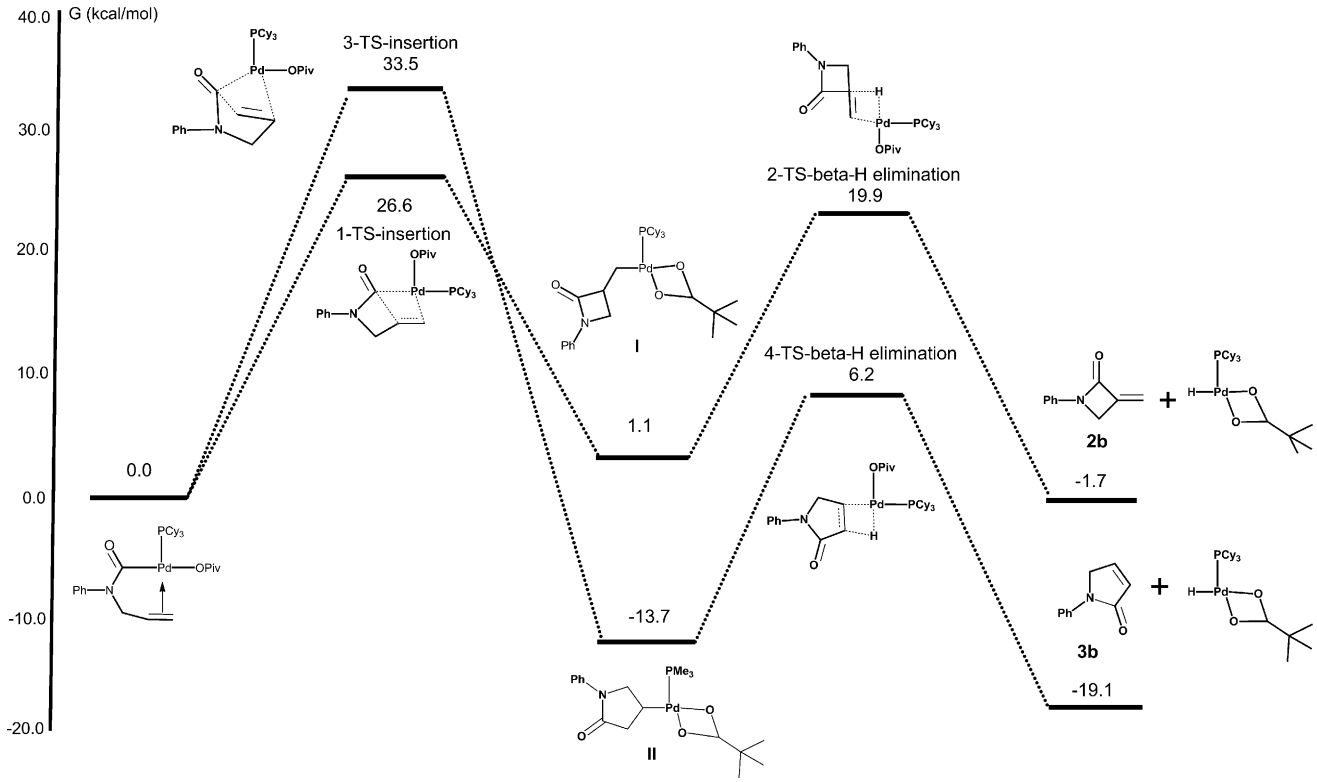

Scheme 5. Free-energy profiles for two competitive reaction pathways.

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