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Palladium-Catalyzed Unactivated C(sp^3)–H Bond Activation and Intramolecular Amination of Carboxamides: A New Approach to β-Lactams

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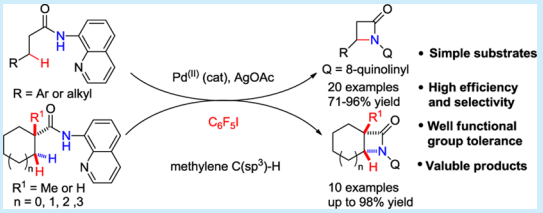
Supporting Information

ABSTRACT: An efficient method to synthesize the β-lactams with high regioselectivity via Pd-catalyzed C(sp^3)–H bond activation and intramolecular amination of simple and readily available aminoquinoline carboxamides was demonstrated. C_6F_5I plays a significant role in the formation of the C–N bond of the four-membered ring β-lactams. High yield along with wide substrate scope and functional group tolerance makes this reaction applicable to build natural-product-derived β-lactams. This method has been applied to the efficient synthesis of the β-lactamase inhibitor MK-8712.



Over the past decade, transition-metal-catalyzed intramolecular amination of the C–H bond has emerged as a straightforward and powerful strategy for the construction of N-heterocyclic compounds, providing an alternative protocol to the traditional cross-coupling reactions.[1−3] Seminal work in 2008 by Yu and co-worker established the procedure for the preparation of γ- and δ-benzo-fused lactams employing Pd-catalyzed intramolecular amination of C–H bonds.[4] Later, the Daugulis,[5] Chen,[6] and Shi[7] groups described a set of Pd-catalyzed, picolinamide- or 1,2,3-triazole-directed, and PhI(OAc)$_2$-mediated intramolecular amination reactions of unactivated C–H bonds of amine substrates to form different kinds of N-heterocycles. Despite these significant advances, there has been no report on metal-catalyzed intramolecular amination of unactivated C(sp^3)–H bonds to build β-lactams. Until recently, during our submission of this paper, the Shi[8] group reported the synthesis of chiral α-amino-β-lactams through Pd-catalyzed sequential monoarylation/amination of C(sp^3)–H bonds. Herein, we report an efficient method to synthesize the various substituted β-lactams with high regioselectivity through Pd-catalyzed C_6F_5I-assisted intramolecular amination of β-C(sp^3)–H bonds of simple and readily available aminoquinoline carboxamides. This method is quite useful for construction of medium-sized ring-fused β-lactams with up to 98% yield. And application for the efficient synthesis of β-lactamase inhibitor MK-8712 is described.

Since the seminal work of Daugulis and co-workers reported Pd-catalyzed arylation of secondary C(sp^3)–H bonds of carboxamides with 8-aminoquinoline (AQ) as directing group,[9] other elegant results have been published by the Corey,[10] Chen,[11] Tobisu and Chatani,[12] Nakamura,[13] and Shi[14,15] groups, relying on the AQ directing group, through palladium- or iron-catalyzed C–C or C–N bond-forming reactions, successively. Encouraged by these elegant success, we envisioned the feasibility to make β-lactams via C–H bond activation methodology, based on mechanistic considerations as following: (1) intermediate similar to **B** (Scheme 2) has been documented in Daugulis[9b] and Corey[10] pioneering work; (2) this reaction is believed most likely to proceed via Pd^{II}/Pd^{IV} process;[1a] (3) two competitive pathways for reductive elimination, can be deduced from intensive research work on electronic effects on reductive elimination to form carbon–carbon and carbon-heteroatom bonds from palladium(II) complexes done by Hartwig and others;[16] (4) fine-tuning of electronic and steric effects of aryl iodides could favor the C–N bond-forming process.

To test our hypothesis, we initiated our studies by examining model substrate **1** with some aryl iodides carrying electron-withdrawing groups in the presence of catalytic Pd(OAc)$_2$ and AgOAc (1.2 equiv) as oxidant.[17] To our surprise, in addition to the cross-coupling product **1c**, we also got two other products-β-lactam **1a** and δ-lactam **1b** (Table 1, entries 1–4). To our delight, the yield of **1a** increased to 65% when 1-iodo-4-nitrobenzene was used without additional solvent (entry 7). We were curious about what would happen to the reaction if 1-iodo-4-nitrobenzene was replaced by a more electron-withdrawing and bulky group substituted aryl iodide such as petanfluoroiodobenzene. In this instance, the reaction proceeded satisfactorily with high regioselectivity to afford only **1a** in moderate yield, and **1b** was not detected (entry 9). Finally, a combination of Pd(OAc)$_2$ (5 mol %), 1.2 equiv of AgOAc, and 5.5 equiv of petanfluoroiodobenzene was

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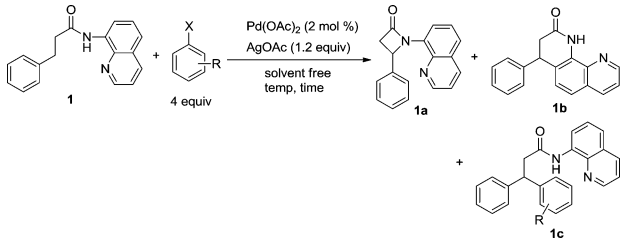
Table 1. Effect with Electron-Withdrawing Substituents of Aryl Iodides on the Reaction



entry	RC_6H_4X	temp (°C), time	yield[a] (%) of **1a**/**1b**/**1c**
1	*p*-AcC_6H_4I	120, 20 min	28/−/58[b]
2	*o*-CF_3 C_6H_4I	120, 24 h	4/4/−[b,e]
3	*p*-CF_3 C_6H_4I	120, 19 h	24/6/−[b,e]
4	*o*-NO_2 C_6H_4I	120, 19 h	25/3/1[b,e]
5	*p*-NO_2 C_6H_4I	THF, 120, 24 h	64/5/20[b]
6	*p*-NO_2 C_6H_4I	toluene, 120,24 h	53/8/26[b]
7	*p*-NO_2 C_6H_4I	170, 15 h	65/−/15[b]
8	*p*-NO_2 C_6H_4Br	120, 24 h	−/5/−[b,e]
9	C_6F_5I	130, 24 h	49/−/−[b,d,f]
10	C_6F_5I	130, 2 h	49/−/−[c,d,f]
11	C_6F_5I	160, 1 h	83/−/−[c,g]
12	C_6F_5I	160, 1.5 h	93/−/−[c,d]

[a]Isolated yield. [b]The reaction was conducted in seal tube. [c]The reaction was run in a CEM microwave reactor, and C_6F_5I (5.5 equiv) was used. [d]$Pd(OAc)_2$ (5 mol %) was used. [e]Most of **1** was recovered. [f]40% of **1** was recovered. [g]$Pd(OAc)_2$ (2.5 mol %) was used, and 13% of **1** was recovered.

established to be the best system for palladium-catalyzed reaction of **1** under microwave for 1.5 h. The effect of various silver salts was also investigated. In addition to AgOAc, Ag_2CO_3, AgF, and AgF_2 were also found to be effective in this reaction to give *β*-lactam product **1a** in 82%, 73%, and 45% yield, respectively. Other silver salts such as Ag_2O and $AgCO_2CF_3$ failed to afford the typical product. Controlled trials showed the reaction did not occur without catalytic $Pd(OAc)_2$ or AgOAc as oxidant.

With the optimized conditions in hand, we investigated the substrate scope of this reaction (Figure 1). First, we tested the substituents on the phenyl ring. The results indicated that this

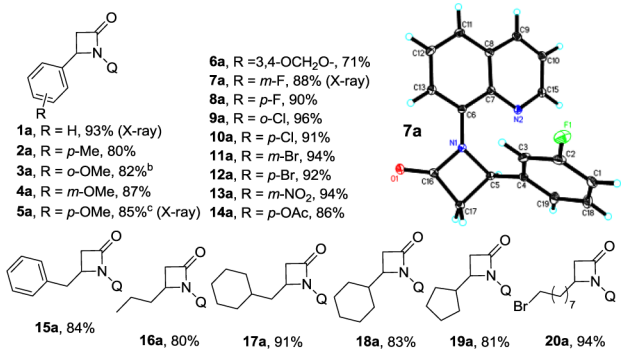


Figure 1. Substrate scope and functional group tolerance. Q = quinolinyl. (a) Unless otherwise specified, all reactions were carried out under conditions A: substrate (0.10 mmol), $Pd(OAc)_2$ (0.005 mmol, 5 mol %), AgOAc (0.12 mmol, 1.2 equiv), C_5F_5I (0.55 mmol, 5.5 equiv), microwave, 160 °C, 1.5 h. Isolated yields. (b) $Pd(OAc)_2$ (7 mol %) was used. (c) $Pd(OAc)_2$ (10 mol %) was used. Reaction time was 5 h.

reaction was not very sensitive to the electron density of the phenyl unit. Both electron-donating and electron-withdrawing groups delivered the corresponding *β*-lactam products (**1a**−**14a**) with good to excellent yields. Generally, electron-donating groups on the phenyl ring slightly decreased the reaction yield. Various functional groups, including MeO (**3a**−**5a**), NO_2 (**13a**), and different halides (**7a**−**12a**) were well tolerated, which provided the opportunities for further functionalization. Moreover, various alkyl-substituted carboxamides were subjected to the reaction conditions to afford the corresponding *β*-lactam products (**15a**−**20a**) with good to excellent yields. The structures several of the *β*-lactam products **1a**, **5a**, and **7a** were unambiguously established by the X-ray single-crystal analysis.[18]

Encouraged by the excellent results from Figure 1, we next examined the carboxamides with different-sized rings. The substrates with various ring units including five-, six-, seven, and eight-membered and bridged ring fragments were suitable for this conversion to furnish the relative cis-fused *β*-lactam products with good to excellent yields. The results are summarized in Figure 2. It strongly indicated that the

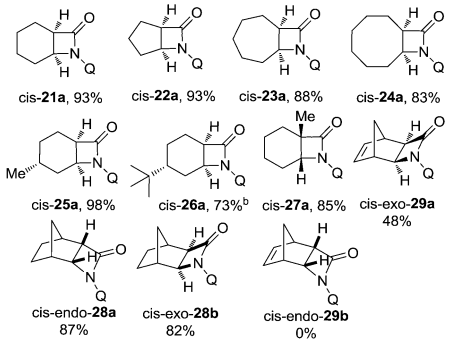


Figure 2. Production of fused *β*-lactams. Q = quinolinyl. (a) Conditions A. (b) $Pd(OAc)_2$ (10 mol %) was used.

configuration of the substrates affected the efficiency of the reaction. For example, the bridged endo-**28** and exo-**28** gave the corresponding relative cis-fused products *cis-endo*-**28a** and *cis-exo*-**28b** in 87% and 82% yields, respectively. The reaction of the *exo*-**29** afforded the product *cis-exo*-**29a** in 48% yield, while *endo*-**29** did not work probably due to the C−C double bond acting as a ligand coordinating to the metal to inhibit the reaction, which is consistent with results from Yu's paper.[19]

We found this method can be applied to some natural-product-related substrates (Figure 3). For instance, **30a** was

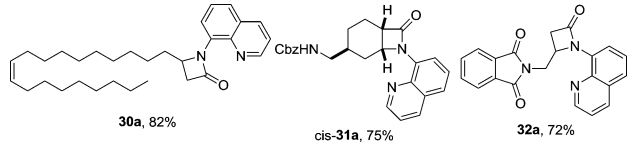


Figure 3. Applications to potential bioactive carboxylic acid derivatives.

obtained in 82% yield under the typical reaction condition from the long-chain natural erucid acid derivative. Interestingly, the middle double bond did not involve in the reaction probably due to the long distance from the reaction center. The all-cis product **31a** was successfully acquired in 75% yield from a natural amino acid derivative. *γ*-Aminobutyric acid (GABA)

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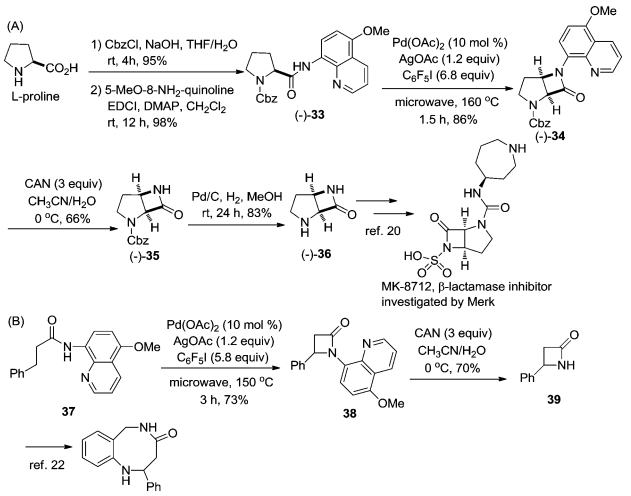
derivative **32** provided the corresponding β-lactam product **32a** in 72% yield under our standard conditions.

To further demonstrate the synthetic utility of this new reaction, we carried out a formal synthesis of MK-8712, a β-lactamase inhibitor investigated by the Merk company (A, Scheme 1).[20] Compound **33** was easily prepared from the

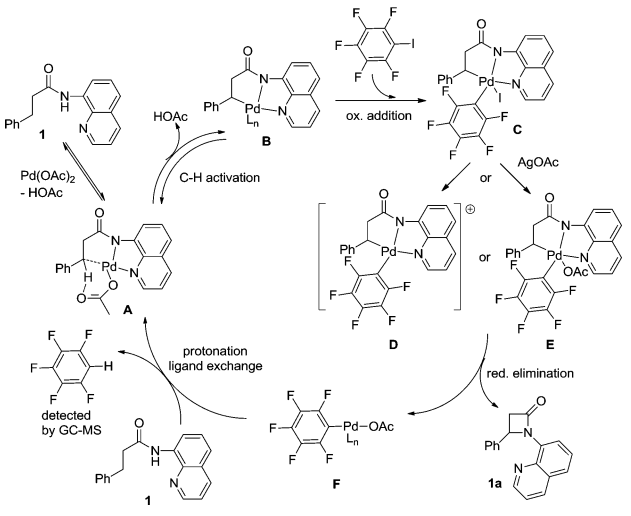
Scheme 1. (A) Formal Synthesis of MK-8712 by MQ Group Directed β-C(sp^3)−H Amination Reaction. (B) Synthesis of Medium-Ring Nitrogen Heterocycles



readily commercial available L-proline. The intramolecular amination reaction of **33** under our standard conditions gave the desired product **34** in 86% yield. The 5-MeO-quinoline (MQ) group[21] of **34** was readily removed upon treatment with CAN, and removal of Cbz group by hydrogenation reaction provided the cis-fused compound **36**, which is the key intermediate for the synthesis of the β-lactamase inhibitor MK-8712. β-Lactam compound **39** was easily synthesized by two steps, which is the building blocks for the synthesis of medium-ring nitrogen heterocycles, macrocyclic spermine, and spermidine alkaloids (B, Scheme 1).[22]

Based on these primary investigations and results from Daugulis'[9b] and Corey's[10] work, a possible reaction mechanism can be provided as shown in Scheme 2. The reaction of

Scheme 2. Plausible Reaction Mechanism



carboxamide **1** with $Pd(OAc)_2$ forms the five-membered palladacycle **A**, which undergoes C−H activation to afford **B**. Oxidative addition of pentafluoroiodobenzene with **B** gives the Pd^{IV} species **C**, which provides **D** or **E** in the presence of AgOAc by ligand exchange. The product **1a** was obtained through reductive elimination, accompanied with intermediate **F**. Then **F** reacts with substrate **1** to produce **A** and release pentafluorobenzene to finish the catalytic cycle. About 1 equiv of pentafluorobenzene was detected by GC−MS in the reaction with model substrate **1** (see more in the Supporting Information).

In summary, we have developed an efficient Pd-catalyzed unactivated β-C(sp^3)−H bond activation and intramolecular amination of 8-aminoquinoline carboxamides to synthesize β-lactams with high regioselectivity. Under our reaction conditions, the reagent of C_6F_5I plays a key role to finely tune the electronic and steric property of reaction intermediates to favor the C−N bond forming process, which is deduced from the excellent experiment results and related references. This method is especially very useful for making β-lactams with a 5/4, 6/4/, 7/4, 8/4 fused ring system, which is rarely achieved by other methodologies. The reaction conditions which are compatible with a broad range of function groups also demonstrated potential application to construct natural-product-derived β-lactams. We have applied this method to an efficient synthesis of key intermediate for the β-lactamase inhibitor MK-8712 successfully. Further mechanistic studies and more applications of this new reaction are now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and mechanism study experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) A pioneering work by Daugulis[9a] showed that the arylation of 8-aminoquinoline-directed carboxamide **1** with 4′-iodoacetophenone afforded the cross-coupling product **1c** in 60% yield accompanied with a byproduct **1b** in 30% yield. Actually, we rechecked this reaction under the exact condition to find that the byproduct should be *β*-lactam **1a**, which was identified unambiguously with full spectrographic and X-ray single-crystal analysis.
(18) The CIF files of **1a**, **5a**, and **7a** have been deposited with Cambridge Crystallographic Data Centre (nos. CCDC 945487, 945489, and 945488). These data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif.
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