Tetrahedron Letters 55 (2014) 3229–3231

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of substituted γ-lactam via Pd(0)-catalyzed cyclization of alkene-tethered carbamoyl chloride

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ARTICLE INFO

Article history:
Received 6 March 2014
Revised 2 April 2014
Accepted 8 April 2014
Available online 13 April 2014

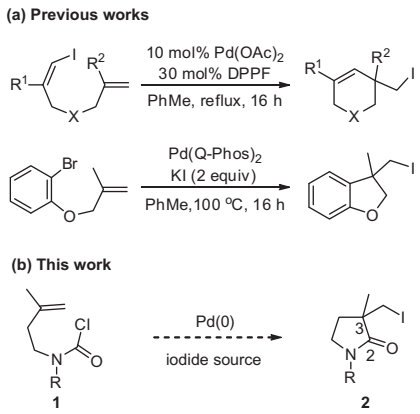
Keywords:
Palladium catalysis
Carboiodonation
Cyclization
γ-Lactam

ABSTRACT

Pd(0)-catalyzed carboiodonation of but-3-enylcarbamic chloride has been developed with NaI as additive, which provides a ready access to substituted γ-lactam bearing an alkyl iodide group. This reaction features alkyl iodide reductive elimination as a key step in catalytic cycle, indicating the crucial role of additive NaI.

γ-Lactams are an important substructure widely occurring in numerous biologically active compounds and natural products.[1] They have proven to be useful building blocks due to their versatile reactivity.[2] Consequently, various efficient methods have been invented for their synthesis. For examples, γ-lactams have been synthesized via addition of nitrogen radical,[3] intramolecular carbenoid C–H insertion,[4] ring expansion of β-lactam,[5] cycloadditions,[6] the imino-Mukaiyama-aldol reaction,[7] and metal-catalyzed cyclizations.[8] Among these reported methods, however, there are few strategies to construct γ-lactam ring via the C2–C3 bond formation.

Recently, we have developed a Pd(0)-catalyzed carboiodonation of vinyl iodide-tethered alkene, which concurrently forms a new C–C bond and C–I bond (Scheme 1a).[9] In 2011, Lautens and coworkers reported an elegant example of Pd(0)-catalyzed carboiodonation of aryl bromide-tethered alkene with the help of KI (Scheme 1a).[10] These two reactions feature the alkyl-Pd(II)-I reductive elimination as the terminating step in catalytic cycle to deliver an alkyl iodide product and to regenerate the Pd(0) catalyst. In sharp contrast to the well-known C–X oxidative addition, the carbon halide reductive elimination has been considered to be a thermodynamically disfavored process.[11] However, some recent developments have clearly demonstrated that this process can be a significantly more common reaction than the previous assumption and has exhibited some advantages toward organic halide synthesis.[12] As our continuous efforts on the Pd(0)-catalyzed carboiodonation,[13] we became interested in the extension of the study to alkene-tethered carbamoyl chloride **1** (Scheme 1b). Herein, we reported the Pd(0)-catalyzed carboiodonation of **1** with the help of a iodide source, which constructs both the C2–C3 bond and the C(alkyl)–I bond to deliver γ-lactam **2** (Scheme 1b).



Scheme 1. Design plan for Pd(0)-catalyzed carboiodonation of **1**.

We commenced our study using compound **1a** as the model substrate. When **1a** was subjected to our previous reaction conditions[9] (10 mol % $Pd(OAc)_2$ and 30 mol % DPPF in refluxing toluene), product **3a** was isolated in 21% yield (Table 1, entry 1). To our delight, the desired carboiodonation product **2a** was obtained in 42% yield with a diastereomeric ratio of 5:1 when 2 equiv of KI

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http://dx.doi.org/10.1016/j.tetlet.2014.04.019
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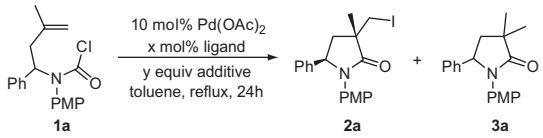
Table 1
Reaction condition's optimization[a]



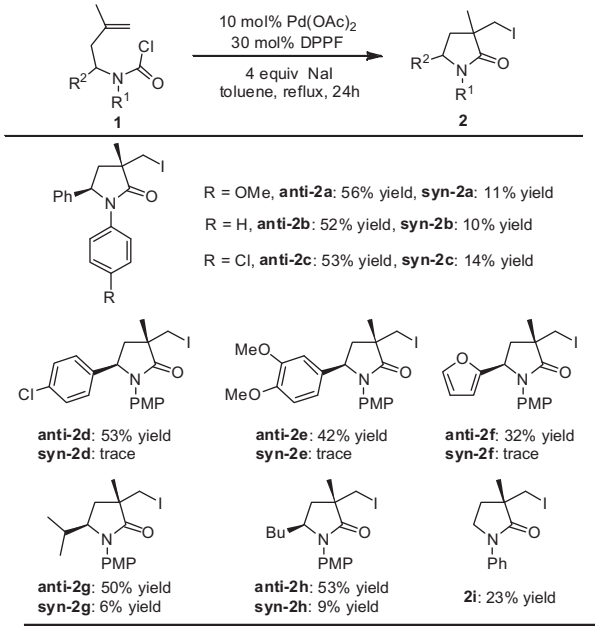
Entry	Ligand (x)	Additive (y)	2a Yield[b] (%)	2a dr[c]	3a Yield[b] (%)
1	DPPF (30)	—	ND	ND	21
2	DPPF (30)	KI (2.0)	42	5:1	6
3	DPPF (30)	LiI (2.0)	ND	ND	ND
4	DPPF (30)	NaI (2.0)	48	5:1	4
5	**DPPF (30)**	**NaI (4.0)**	**67**	**5:1**	**12**
6	DPPF (30)	NaI (6.0)	51	5.4:1	14
7	$(Ad)_2P(Bu)$[d]	NaI (4.0)	44	5.3:1	6
8	$(^tBu)_3P$[d]	NaI (4.0)	25	2.6:1	5

The bold format means the optimized conditions.
[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.06 mmol), 3 mL toluene.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude reaction mixture.
[d] 60 mol % ligand was used.

was added (Table 1, entry 2). The anti-isomer was unambiguously identified as the major product on the basis of NOE NMR experiments (see Supporting information). These results clearly demonstrated the importance of external iodide source. Thus, different iodide sources were further tested. LiI (2 equiv) was found to inhibit the reaction and 88% of substrate **1a** was recovered (Table 1, entry 3). NaI (2 equiv) gave a somewhat better result, increasing the yield of **2a** to 48% (Table 1, entry 4). The isolated yield of **2a** could be further improved to 67% when the NaI loading was increased to 4 equiv (Table 1, entry 5). However, increasing the loading of NaI to 6 equiv caused a decrease in yield (51%) while the diastereoselectivity was improved to 5.4:1 (Table 1, entry 6). Ligand screening disclosed that sterically hindered monodentate-phosphines $(Ad)_2P(Bu)$ and $(tBu)_3P$ were also able to realize this transformation although the corresponding yields were 44% and 25%, respectively (Table 1, entries 7 and 8). At this stage, we could not improve the reaction performance, with respective to yield and diastereoselectivity, although other reaction parameters, such as ligand, catalyst precursor, as well as solvent, were thoroughly investigated (see Supporting information).

With the optimized catalytic conditions in hand, we then explored the effect of N-substituent at the carbamoyl chloride moiety. We were pleased to find that a variety of *N*-aryl carbamoyl chlorides **1a**–**1c** proved to be suitable substrates with optimal results being accomplished with N-PMP substituted substrate **1a** (Scheme 2).

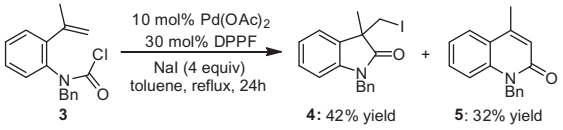
Subsequently, we tested the scope of the Pd(0)-catalyzed carboiodonation with respect to N-PMP substituted carbamoyl chlorides **1** and the results are summarized in Scheme 2. The transformation proceeded smoothly to afford the desired products in moderate yields as well as moderate to high level of diastereoselectivity. More importantly, from the synthetic point of view, the resultant two isomers could be easily separated by silica gel column chromatography. For the substituent R^2, reactions tolerated the installations of not only electron-deficient and electron-rich benzene rings (Scheme 2, **2d** and **2e**) but also a furyl moiety (Scheme 2, **2f**). Albeit in moderate yields, these three cases only produced anti products, showing high diastereoselectivity. Alkyl groups could also be installed at the R^2 position. Butyl-substituted **2h** was isolated in 62% yield and with 6:1 diastereoselectivity and *i*-propyl containing **2g** was obtained with the yield of 56% and dia-



Scheme 2. The reaction scope. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), DPPF (0.06 mmol), 3 mL toluene.

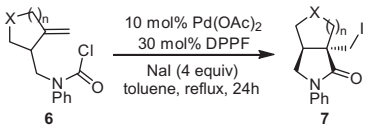
stereoselectivity of 8:1 (Scheme 2). Likely due to the lack of the Thorpe–Ingold effect, the cyclization of the substrate with $R^2 = H$ afforded product **2i** only in the yield of 23%. It should be noted that ca. 10% yield of the corresponding hydrolysis product was concurrently isolated for every case.

To our delight, five-membered benzo-fused lactam **4** was also readily isolated in the yield of 42% when compound **3** was employed as a substrate under these reaction conditions (Eq. 1). Along with the carboiodonation product **4**, Heck-reaction product **5**[14] was obtained in 32% yield likely via the fashion of 6-endo cyclization.



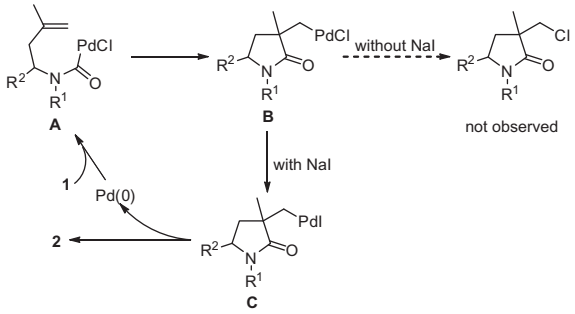
(1)

This methodology was further applied to the synthesis of bicyclic lactams **7** (Scheme 3). The starting materials **6a**–**6c** were readily synthesized in three steps (See Supporting information). Cyclopentane-fused lactam **7a** was obtained in 47% yield (Scheme 3, entry 1) while cyclohexane-fused analogue **7b** was isolated as a single diastereomer in somewhat better yield (Scheme 3, entry 2). Remarkably, this reaction is tolerant toward N-atom. Indeed, piperidine-fused lactam **7c** was also formed as a single diastereomer in 55% yield (Scheme 3, entry 2).

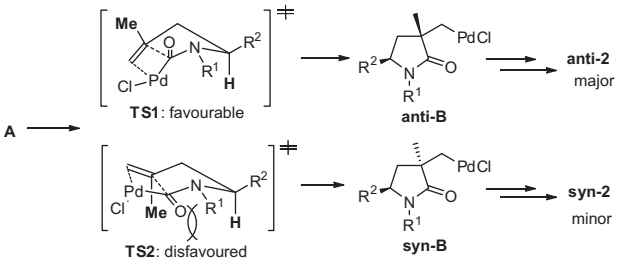


entry	6 (X, n)	7 (yield)
1	**6a** (X = CH_2, n = 1)	**7a** (47%)
2	**6b** (X = CH_2, n = 2)	**7b** (63%)
3	**6c** (X = NBoc, n = 2)	**7c** (55%)

Scheme 3. The synthesis of bicyclic lactams.



Scheme 4. The proposed mechanism.



Scheme 5. Rational for the observed stereoselectivity.

Although we could not provide further details to elucidate the precise reaction mechanism, a proposal is present in Scheme 4. On the basis of the well-known metal-catalyzed transformations of carbamoyl chloride,[15] we believed that the reaction would be initiated by oxidative addition of carbamoyl chloride **1** to Pd(0) center, resulting in the formation of intermediate **A**. Then, alkyl-Pd(II)-Cl intermediate **B** is formed via intramolecular insertion of alkene into the carbonyl-Pd(II) bond of intermediate **A**. After ligand exchange between chloride and iodide, intermediate **B** is converted to alkyl-Pd(II)-I intermediate **C**, which is followed by reductive elimination of alkyl-Pd(II)-I to yield alkyl iodide product **2** and regenerate the Pd(0) catalyst. The fact that the corresponding alkyl chloride product could not be detected without external iodide source strongly demonstrated that alkyl chloride reductive elimination should be much less efficient than the iodide case. This observation is consistent with Houk's computational study on the alkyl halide reductive elimination.[16]

The observed stereoselectivity is believed to be determined by the process of alkene insertion, in which the transition state **TS1** might be more favorable than **TS2** in order to the minimize the axial–axial interaction between Me and H groups (Scheme 5). Thus, the former would lead to **anti-2** as the major product.

In summary, we have developed the Pd(0)-catalyzed carboiodonation of alkene-tethered carbamoyl chloride with the help of NaI, which provides a facile method for the synthesis of substituted γ-lactams. The fact that no reaction occurred without additive NaI clearly indicated that it plays a crucial role in this transformation. The further application of this finding to develop asymmetric synthesis of substituted γ-lactam is currently under investigation.

Acknowledgments

We thank NSFC (Nos. 21002025 and 21272066), the Fundamental Research Funds for the Central Universities, Fok Ying-Tong Education Foundation for Young Teachers in the Higher Education Institutions of China (131011), and NCET (No. 12-0851) for funding this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.019.

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