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Preference of β-Lactam Formation in Cu(I)-Catalyzed Intramolecular Coupling of Amides with Vinyl Bromides

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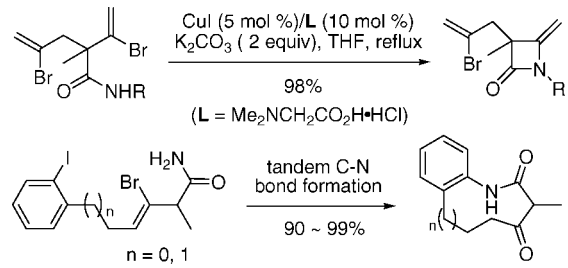
ABSTRACT



A general and highly efficient synthesis of 4-alkylidene-2-azetidinones was achieved by the Cu(I)-catalyzed intramolecular C−N coupling of amides with vinyl bromides. This 4-*exo* ring closure was found to be fundamentally preferred over other modes (5-*exo*, 6-*exo*, and 6-*endo*) of cyclization under copper catalysis. Tandem C−N bond formation was then successfully developed to allow the convenient generation of medium-sized lactams.

β-Lactams are an intensively studied family of heterocycles primarily because of their biological activity.[1] For example, β-lactam antibiotics such as penicillins and cephalosporins have occupied a central role in the fight against pathogenic bacteria.[1] In the meantime, β-lactams serve as versatile building blocks in synthetic organic chemistry.[2] As a consequence, the synthesis of β-lactams has received enormous attention, and considerable progress has been achieved.[1,2]

4-Alkylidene-2-azetidinones are a group of β-lactams with important biological interest.[3] As compared to other β-lactam inhibitors, this novel structure was responsible for an increased inhibition of human leukocyte elastase, a very potent degradative weapon released by inflammatory cells.[3] Some 4-alkylidene-β-lactams showed promising antibiotic activity against resistant bacteria.[3a] Furthermore, they were the first β-lactams shown to be active at micromolar concentrations against two matrix metalloproteases instrumental in cancer invasion and metastasis, MMP-2 and MMP-9.[3c] In addition to their biological activity, 4-alkylidene-2-azetidinones, as cyclic enamides, are also useful synthetic intermediates due to their unique combination of functional groups. However, there is a scarcity of methods for their preparation. Bachi et al. reported the synthesis of 4-alkylidene-2-azetidinones via rhodium-catalyzed reactions of 4-thioxo-2-azetidinones with diazo compounds.[4] Cainelli and

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(2) For a comprehensive review, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.

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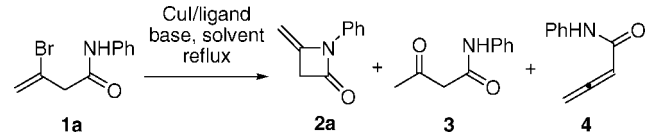
co-workers found that the Lewis acid mediated reactions of 4-acetoxy-2-azetidinones with acyldiazo compounds led to the generation of 4-(2-oxoethylidene)-β-lactams.[5] Fustero et al. showed that palladium-catalyzed intramolecular hydroamination of difluoropropargyl amides afforded fluorinated β-lactams.[6] However, both *Z*- and *E*-isomers were obtained, and the method is limited to α,α-difluoro-substituted amides. It is therefore of interest to develop general and efficient methods for the synthesis of 4-alkylidene-β-lactams. Herein we report a highly efficient and convenient approach to these molecules via Cu(I)-catalyzed intramolecular N-vinylation of amides.

The formation of aryl C−N bonds via copper-catalyzed Ullmann coupling between aryl halides and N-centered nucleophiles has received considerable attention in the past few years.[7] The high stability and low cost of the copper catalysts enable these transformations to be a useful complement to the more extensively investigated Pd(0)-catalyzed processes.[8] By the appropriate choice of copper source, ligand, base, and reaction temperature, these coupling reactions have been developed to include a wide range of substrates under mild conditions. This method was successfully extended to vinylic C−N bond formation and found important application in natural product synthesis.[9] During our investigation on Cu(I)-catalyzed intramolecular vinylation reactions,[10] we found that, with CuI as the catalyst and *N*,*N*′-dimethylethylenediamine as the ligand, a number of iodoalkenamides underwent cyclization in refluxing dioxane, leading to the formation of five-, six-, and even seven-membered lactams.[10b] It is certainly highly desirable to extend this method to the synthesis of 4-alkylidene-β-lactams.[11] However, our initial trial with 3-iodobut-3-enamide under the abovementioned conditions failed to give the desired β-lactam product.[10b] The reaction was rather complicated while all the starting material was consumed.

To explore the possible β-lactam formation under Cu(I) catalysis, we then chose *N*-phenyl-3-bromobut-3-enamide (**1a**) as the model substrate and carried out the optimization of reaction conditions (Table 1). Substrate **1a** was first subjected to the following typical Ullmann coupling conditions: CuI (20 mol%), *N*,*N*′-dimethylethylenediamine (**A**, 40 mol%), Cs_2CO_3 (2 equiv) in refluxing dioxane. The reaction was complete within 3 h, and the expected β-lactam **2a** was isolated in only 13% yield along with the formation of β-ketoamide **3** (25%) (entry 1, Table 1). Switching the base to K_2CO_3 increased the yields of both **2a** and **3** (entry 2, Table 1). Thinking that **3** might result from the decomposition of **2a**, we lowered the reaction temperature. To our delight, **2a** was achieved in 70% yield when the reaction was conducted in refluxing THF. K_2CO_3 was again proven to be superior over Cs_2CO_3 and K_3PO_4 (entries 3−5, Table 1). We next screened the ligands.[12] Changing the ligand **A** to 1,10-phenanthroline (**B**) resulted in the generation of allene

Table 1. Optimization of the Synthesis of **2a** from **1a**



				yield (%)[c]		
entry	ligand[a]	base	solvent/time[b]	**2a**	**3**	**4**
1	**A**	Cs_2CO_3	dioxane (3 h)	13	25	0
2	**A**	K_2CO_3	dioxane (3 h)	38	40	0
3	**A**	K_2CO_3	THF (12 h)	70	25	0
4	**A**	Cs_2CO_3	THF (12 h)	10	20	0
5	**A**	K_3PO_4	THF (12 h)	16	21	0
6	**B**	K_2CO_3	THF (16 h)	0	0	86
7	**C**	K_2CO_3	THF (16 h)	69	6	9
8	**D**	K_2CO_3	THF (16 h)	25	23	30
9	**E**	K_2CO_3	THF (16 h)	91	0	6
10[d]	**E**	K_2CO_3	THF (17 h)	94	0	4
11[e]	**E**	K_2CO_3	THF (17 h)	94	0	0
12	none	K_2CO_3	THF (16 h)	17	63	16

[a] **A**: *N*,*N*′-dimethylethylenediamine. **B**: 1,10-phenanthroline. **C**: 2-isobutyrylcyclohexanone. **D**: L-proline. **E**: $Me_2NCH_2CO_2H$·HCl. [b] Reaction conditions: **1a** (0.3 mmol), CuI (0.06 mmol), ligand (0.12 mmol), base (0.6 mmol), solvent (10 mL), reflux. [c] Isolated yield based on **1a**. [d] 10 mol % of CuI and 20 mol % of **E** were used. [e] 5 mol % of CuI and 10 mol % of **E** were used.

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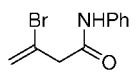
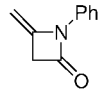
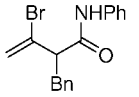
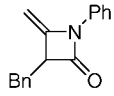
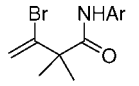
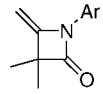
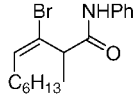
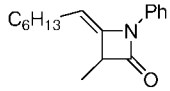
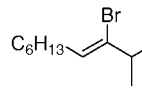
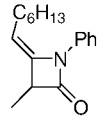
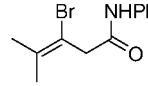
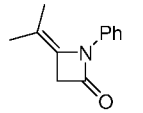
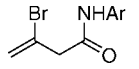
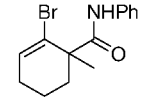
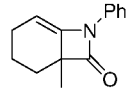
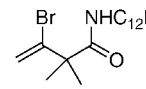
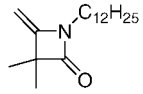
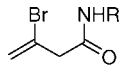
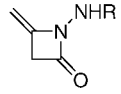
(11) Joyeau et al. reported the formation of β-lactams via the treatment of 3-bromo-3-butenamides with copper metal (5 equiv) in DMF at 130−135 °C. See: Joyeau, R.; Kobaiter, R.; Sadet, J.; Wakselman, M. *Tetrahedron Lett.* **1989**, *30*, 337.

4 rather than **2a** (entry 6, Table 1). On the other hand, *N*,*N*-dimethylglycine hydrochloride (**E**) turned out to be the best ligand (entries 5−9, Table 1). The cyclization of **1a** proceeded smoothly to afford **2a** in an excellent yield even when the amount of CuI was reduced to 5 mol % (entry 11, Table 1).

Table 2. Synthesis of 4-Alkylidene-2-azetidinones **2**

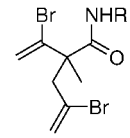
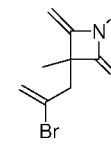
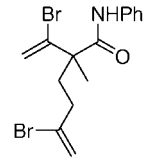
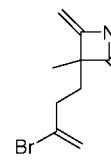
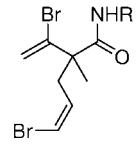
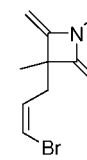
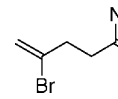
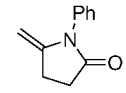
entry[a]	substrate	product (time, yield)[b]
1	 **1a**	 **2a** (17 h, 94%)
2	 **1b**	 **2b** (18 h, 99%)
3	 **1c** (Ar = Ph)	 **2c** (18 h, 99%)
4	**1d** (Ar = *p*-CO_2Me-C_6H_4)	**2d** (20 h, 99%)
5	 **1e**	 **2e** (28 h, 97%)
6	 **1f**	 **2f** (32 h, 97%)
7[c]	 **1g**	 **2g** (24 h, 98%)
8	 **1h** (Ar = *p*-Me-C_6H_4)	 **2h** (18 h, 98%)
9	**1i** (Ar = *p*-MeO-C_6H_4)	**2i** (16 h, 99%)
10[c]	 **1j**	 **2j** (21 h, 99%)
11	 **1k**	 **2k** (35 h, 95%)
12	 **1l** (R = Bn)	 **2l** (16 h, 92%)
13[c]	**1m** (R = *c*-C_6H_{11})	**2m** (24 h, 70%)

[a] Reaction conditions: **1** (0.3 mmol), CuI (2.9 mg, 0.015 mmol), **E** (4.2 mg, 0.03 mmol), K_2CO_3 (83 mg, 0.6 mmol), THF (3 mL), reflux. [b] Isolated yield based on **1**. [c] The reaction was conducted in refluxing acetonitrile.

With the optimized conditions in hand (5 mol % of CuI, 10 mol % of **E**, 200 mol % of K_2CO_3 in refluxing THF), we then examined the generality of this method. The results are summarized in Table 2. Substrates with various substitution patterns all gave the expected β-lactams in almost quantitative yield. The configuration of the C=C double bond was nicely retained, as evidenced by the reactions of **1e** and **1f**. Functional groups such as CO_2Me (in **1d**) and OMe (in **1i**) were well tolerated. The *N*-alkyl-substituted amides showed similar behavior as the *N*-aryl ones, although bulkier *N*-alkyl groups might slow down the coupling (entry 13, Table 2).

The above results clearly illustrated the ease of C−N coupling via a 4-*exo* ring closure under copper catalysis. As a comparison, *N*-phenyl-4-bromopent-4-enamide (**5g**) was prepared and subjected to the same conditions in Table 2. After 24 h reflux in THF, only a trace amount of the expected product via a 5-*exo* ring closure could be detected, while most of the starting material remained unchanged (see also Table 3). This strongly implied that 4-*exo* cyclization is more

Table 3. Preference of 4-*exo* Ring Closure

entry[a]	substrate	product (time, yield)[b]
1	 **5a** (R = Ph)	 **6a** (18 h, 99%)
2	**5b** (R = Bn)	**6b** (17 h, 98%)
3	 **5c** (R = Ph)	 **6c** (19 h, 99%)
4	**5d** (R = Bn)	**6d** (25 h, 97%)
5	 **5e** (R = Ph)	 **6e** (19 h, 99%)
6	**5f** (R = Bn)	**6f** (24 h, 96%)
7	 **5g**	 **6g** (24 h, trace)

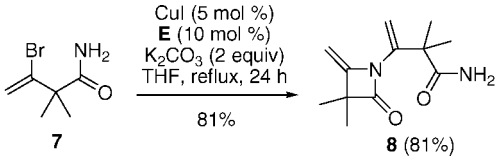
[a] Reaction conditions: **5** (0.3 mmol), CuI (2.9 mg, 0.015 mmol), **E** (4.2 mg, 0.03 mmol), K_2CO_3 (83 mg, 0.6 mmol), THF (3 mL), reflux. [b] Isolated yield based on **5**.

favorable than 5-*exo* cyclization. To have a direct competition among different modes of cyclization, substrates **5a**−**f**, each having two possible modes of cyclization, were synthesized and their reactions under the above optimized conditions were performed. In each case, only the 4-*exo* cyclization product was obtained in almost quantitative yield, while the competing 5-*exo* (entries 1 and 2), 6-*exo* (entries 3 and 4), or 6-*endo* (entries 5 and 6) cyclization product was not observed at all (Table 3). The results in Table 3 unambiguously demonstrated the preference of β-lactam formation in the intramolecular C−N coupling processes. This observation, along with our previous finding in the intramolecular C−O coupling of alcohols with vinyl bromides,[10d] strongly

(12) *N*,*N*′-Dimethylethylenediamine: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. 1,10-Phenanthroline: Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. 2-Isobutyrylcyclohexanone: Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8762. L-Proline: Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. *N*,*N*-Dimethylglycine hydrochloride: Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799.

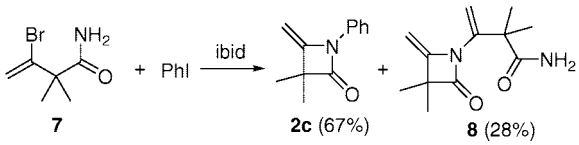
implies that the preference of the uncommon 4-*exo* cyclization is in fact a common phenomenon in Cu(I)-catalyzed coupling processes. Although the reason for such a preference remains unclear, it could be possible that the transition state for 4-*exo* cyclization as a Cu-containing five-membered ring is kinetically and thermodynamically more favorable. Theoretical analyses on this assumption are currently underway in our laboratory and will be reported in due course.

The above reactions dealt with *N*-aryl- or *N*-alkyl-substituted amides. We then turned our attention to the behavior of primary amides. Interestingly, the treatment of substrate **7** under the optimized conditions afforded β-lactam **8** in 81% yield (eq 1), which apparently resulted from double N-vinylation (intramolecularly and intermolecularly). No monovinylation product could be detected, implying that the intermolecular coupling is of comparable rate to the intramolecular coupling. This double C−N bond formation[13] could then be extended to the bimolecular cases exemplified by the reaction of **7** with 2 equiv of iodobenzene (eq 2). The desired coupling product **2c** was generated in 67% yield along with the formation of **8** in 28% yield.



(1)

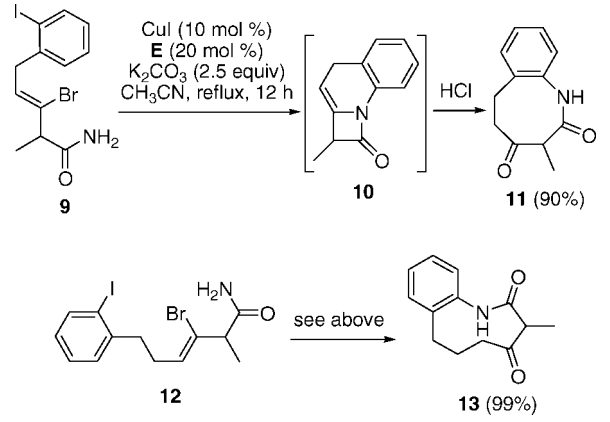
The ease of 4-*exo* cyclization and double C−N bond



(2)

formation shown above should find important application in organic synthesis. As an example, the copper-catalyzed reaction of primary amide **9** followed by the subsequent hydrolysis with aqueous hydrochloric acid led to the efficient synthesis of 8-membered lactam **11** (Scheme 1). Presumably the amide **9** underwent 4-*exo* cyclization followed by the intramolecular N-arylation to give the unstable tricyclic intermediate **10**. The hydrolytic cleavage of the enamide C−N bond afforded the ring expansion product **11**. As an extension of this method, the 9-membered lactam **13** was achieved from amide **12** in almost quantitative yield.

Scheme 1. Synthesis of Medium-Sized Lactams via Copper-Catalyzed Tandem C−N Bond Formation



In conclusion, we have developed a general and highly efficient method for the synthesis of 4-alkyliden-2-azetidinones via copper-catalyzed intramolecular C−N coupling of 3-bromobut-3-enamides. More importantly, this 4-*exo* ring closure is fundamentally preferred over other modes of cyclization, illustrating the unique property of Cu(I)-catalysis. This method also allows the convenient synthesis of medium-sized lactams via tandem C−N bond formation.

Acknowledgment. This project was supported by the National NSF of China (Grant 20672136, 20702060 and 20772142) and by the Shanghai Municipal Committee of Science and Technology (Grant 07XD14038).

Supporting Information Available: Characterizations of **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801545A

(13) For examples of copper-catalyzed double C−N bond formation, see: (a) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (b) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653. (c) References 9f and 9i.