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General and Highly Efficient Synthesis of 2-Alkylideneazetidines and β-Lactams via Copper-Catalyzed Intramolecular N-Vinylation

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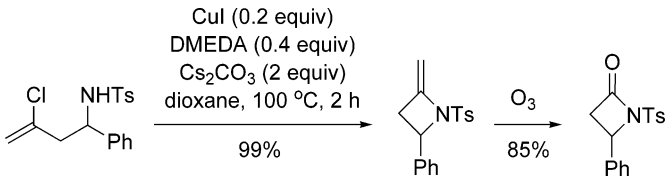
ABSTRACT



***N*-Tosyl-3-halo-3-butenylamines underwent efficient Ullmann-type coupling with the catalysis of CuI/*N*,*N*′-dimethylethylenediamine to afford 2-alkylideneazetidines, which could be readily converted to the corresponding β-lactams by oxidation with O_3.**

Small-ring nitrogen heterocycles are of considerable interest not only because of their wide use as important synthetic intermediates but also because of their biological activities such as antibiotic properties. Among them, the four-membered azetidine series, especially azetidin-2-ones (β-lactams), has gained enormous attention.[1] However, the formation of a four-membered ring system is difficult mainly because of the Dunitz−Schomaker strain, which is significant in four-membered rings but does not exist in three-membered rings.[2] Despite the significant progress achieved in this field, the development of convenient, general, and synthetically useful methodologies for azetidines is still highly desirable.

The formation of aryl C−X bonds (X = O, S, N, etc.) via copper-catalyzed Ullmann coupling between aryl halides and heteroatom-centered nucleophiles has received considerable attention in the past few years.[3] The high stability and low cost of the copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium-catalyzed processes.[4] By the appropriate combination of copper source, ligand, base, and solvent, these coupling reactions have been developed to include a wide range of substrates under mild conditions.[5] This methodology was successfully extended to vinylic C−X bond formation and found important application in natural product synthesis. However, to the best of our knowledge, no copper- or even palladium-catalyzed C−N bond formation via a four-membered ring closure has been reported.[6] We were motivated to explore this possibility owing to our interest in the copper-catalyzed intramolecular vinylation.[7] Herein, we wish

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(4) For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negichi, E.-i., Ed.; Wiley: New York, 2002; Vol. 1, p 1051. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (e) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J. -F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (g) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (h) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

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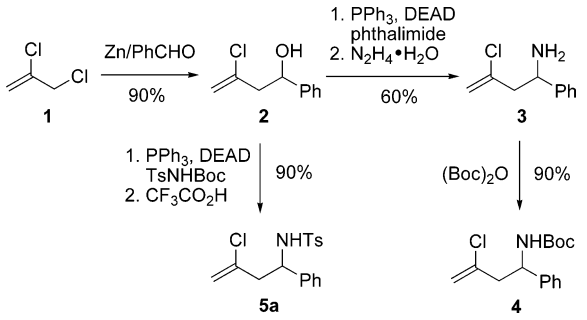
to report that the copper-catalyzed Ullmann-type coupling of *N*-tosyl-3-halo-3-butenamines provides an extremely efficient entry to 2-alkylideneazetidines and, by subsequent oxidation with O_3, to β-lactams.

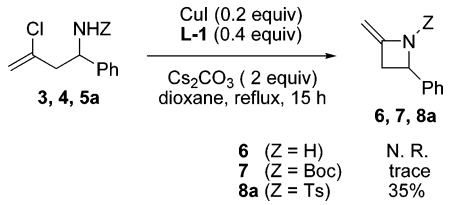
We first chose 3-chloro-3-butenylamines **3**, **4**, and **5a** as the substrates. These compounds could be readily prepared from the commercially available 2-chloroallyl chloride **1** by zinc-mediated condensation with benzaldehyde (to give **2**) followed by Mitsunobu reactions (Scheme 1). We then

Scheme 1. Synthesis of Substrates **3a**, **4**, and **5**



subjected them to the treatment of a typical Ullmann coupling condition: CuI (20 mol %), *N*,*N*-dimethylglycine hydrochloride (**L-1**, 40 mol %), and Cs_2CO_3 (2 equiv) in dioxane, respectively. The mixture was refluxed for 15 h. No reaction was observed for amine **3**. For Boc-protected amide **4**, only a trace amount of the desired product **7** could be detected. To our delight, when sulfonamide **5a** was used as the substrate, the expected product **8a** was achieved in 35% yield (Scheme 2).

Scheme 2. Copper-Catalyzed Cyclization of **3**, **4**, and **5a**



We then conducted a brief optimization of reaction conditions for **5a**, and the results are summarized in Table

Table 1. Optimization of the Synthesis of **8a** from **5a**

entry[a]	ligand[b]	base	time (h)	yield (%)[c]
1	–	Cs_2CO_3	15	0
2	**L-1**	Cs_2CO_3	15	35
3	**L-2**	Cs_2CO_3	15	5
4	**L-3**	Cs_2CO_3	15	<5
5	**L-4**	Cs_2CO_3	15	27
6	**L-5**	Cs_2CO_3	2	99
7	**L-5**	K_2CO_3	2	99
8	**L-5**	K_3PO_4	2	87
9[d]	**L-5**	Cs_2CO_3	15	9

[a] Reaction conditions: **5a** (0.3 mmol), CuI (0.06 mmol), ligand (0.12 mmol), base (0.6 mmol), dioxane (10 mL), reflux. [b] **L-1**: $Me_2NCH_2CO_2H$•HCl. **L-2**: L-proline. **L-3**: 2-aminoethanol. **L-4**: 1,10-phenanthroline. **L-5**: *N*,*N*′-dimethylethylenediamine. [c] Isolated yield based on **5a**. [d] The reaction was run at 80 °C.

1. The choice of ligand proved to be critical to the coupling (entries 1−6, Table 1). Without the aid of a ligand, no reaction occurred (entry 1, Table 1). Among the frequently used ligands screened (**L-1**−**L-5**), *N*,*N*′-dimethylethylenediamine **L-5** gave the best performance. The reaction was clean and fast when **L-5** was used as the ligand, and the product **8a** was achieved in almost quantitative yield (entry 6, Table 1). No intermolecular coupling products could be detected. Interestingly, no significant difference was observed when the base was switched from Cs_2CO_3 to K_2CO_3 or K_3PO_4 (entries 6−8, Table 1). Lowering the temperature to 80 °C resulted in a much slower reaction (entry 9, Table 1). As a comparison, under the optimized conditions (entry 6, Table 1), amide **4** afforded the product **7** in 55% yield and amine **3** remained unchanged. These different reactivities are in parallel with the acidities of the N−H protons in the substrates.

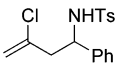
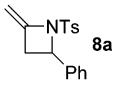
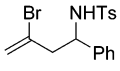
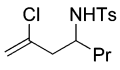
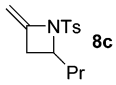
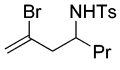
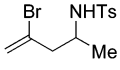
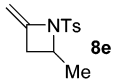
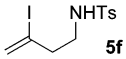
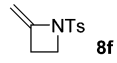
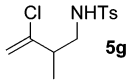
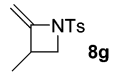
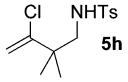
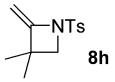
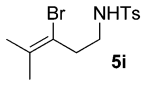
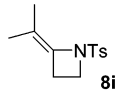
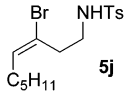
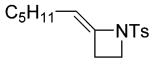
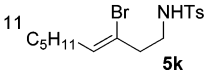
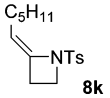
We then prepared a number of *N*-(3-halo-3-buten-1-yl)-sulfonamides **5a**−**k** and carried out their cyclization reactions under the catalysis of CuI. The results are summarized in Table 2. With the bromo analogue of **5a**, vinyl bromide **5b**, as the substrate, the reaction could be performed under much milder conditions (entry 2, Table 2). The reaction was complete at a lower temperature within a shorter time (1 h) with the use of less CuI. With vinyl iodide **5f** as the substrate, the reaction took place even at room temperature. When the temperature was raised to 40 °C, the reaction was complete within 2 h and the product **8f** was obtained in 94% yield (entry 6, Table 2). Substrates of various substitution patterns all underwent cyclization smoothly to afford the expected 2-alkylideneazetidines in excellent yields. Moreover, the configuration of the C=C double bond was nicely retained as evidenced by the reactions of **5j** and **5k** (entries 10 and 11, Table 2).

(5) For the latest selected examples, see: (a) Gorobets, E.; McDonald, R.; Keay, B. A. *Org. Lett.* **2006**, *8*, 1483. (b) Cai, Q.; He, G.; Ma, D. *J. Org. Chem.* **2006**, *71*, 5268. (c) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (d) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779. (e) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274. (f) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (g) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J. *Chem.−Eur. J.* **2006**, *12*, 5301. (h) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.−Eur. J.* **2006**, *12*, 3636. (i) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (j) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (k) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (l) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026. (m) Alcalde, E.; Dinarès, I.; Rodríguez, S.; Miguel, C. G. *Eur. J. Org. Chem.* **2005**, *8*, 1637. (n) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (o) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948.

(6) 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. However, our attempts in the Cu(I)-catalyzed coupling reactions of 3-iodo-3-butenamides failed. See ref 7b.

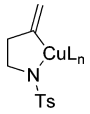
(7) (a) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427. (b) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (c) Fang, Y.; Li, C. *Chem. Commun.* **2005**, 3574.

Table 2. Synthesis of Azetidines **8**

entry	substrate	CuI (mol%)	temp./time (°C / h)[a]	product	yield (%)[b]
1	 **5a**	20	100 / 2	 **8a**	99
2	 **5b**	10	68 / 1	**8a**	99
3	 **5c**	20	100 / 2	 **8c**	99
4	 **5d**	10	68 / 1	**8c**	99
5	 **5e**	10	68 / 1	 **8e**	99
6	 **5f**	10	40 / 2	 **8f**	94
7	 **5g**	20	100 / 5	 **8g**	99
8	 **5h**	20	100 / 3	 **8h**	99
9	 **5i**	20	68 / 6	 **8i**	99
10	 **5j**	20	68 / 3	 **8j**	86
11	 **5k**	20	68 / 12	 **8k**	89

[a] 100 °C and 68 °C refer to the refluxing temperatures of dioxane and THF, respectively. [b] Isolated yield based on **5**.

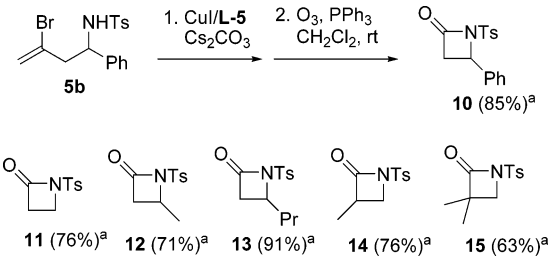
The above results clearly demonstrated the high efficiency of the four-membered ring closure. Presumably, this might be rationalized by the possible transition state **9** which, as a five-membered ring, could be favorable sterically and thermodynamically.



9

The convenient synthesis of 2-alkylideneazetidines as a unique class of strained cyclic enamines should have important applications in organic synthesis, although little is known of their chemistry because of their difficult preparation.[8] As an example, we show here that these compounds could be readily converted to the corresponding β-lactams in high yields by a conventional O_3 oxidation procedure[9] (Scheme 3).

Scheme 3. Synthesis of β-Lactams **10**−**15**



[a] Isolated yield based on **5**.

Thus, the above Ullmann coupling−oxidation processes constitute an efficient and general entry to the synthesis of β-lactams.[10]

Acknowledgment. This project was supported by the National NSF of China (Nos. 20325207 and 20472109) and by the Shanghai Municipal Committee of Science and Technology (No. 04QMH1418).

Supporting Information Available: Synthesis and characterizations of **2**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Hon, Y.; Lin, S.; Lu, L.; Chen, Y. *Tetrahedron* **1995**, *51*, 5019.

(10) For reviews on the synthesis of β-lactams, see: (a) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (c) *Synthesis of β-Lactam Antibiotics: Chemistry, Biocatalysis and Process Integration*; Bruggink, A., Ed.; Kluwer: Dorfrecht, 2001. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (e) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; VCH: New York, 1997.