Synthesis of Heterocycles Based on Rhodium-Catalyzed C–H Amination

Keisuke Takahashi, Daisuke Yamaguchi, Jun Ishihara, Susumi Hatakeyama*

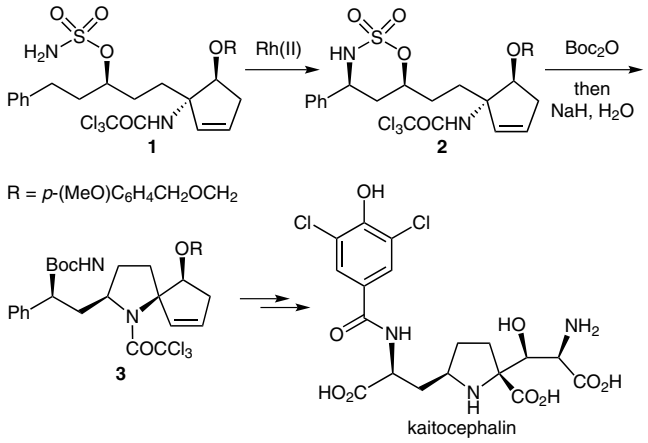
Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
Fax +81(95)8192426; E-mail: susumi@nagasaki-u.ac.jp

Received: 26.08.2013; Accepted after revision: 25.09.2013

Abstract: A new stereoselective approach to substituted pyrrolidines and piperidines is described that involves Du Bois' C–H amination reaction, Boc-activation of a cyclic sulfamate group, and base-promoted intramolecular cyclization. This methodology can be utilized for the synthesis of tetrahydrofuran and tetrahydrothiophene derivatives.

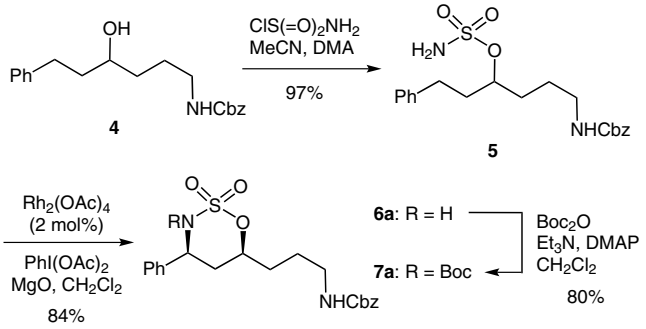
Key word: C–H amination, heterocycle synthesis, rhodium-catalyzed reaction, cyclization

Developing new methodologies for the synthesis of heterocyclic compounds is of great importance in drug discovery, material science, and natural product synthesis.[1,2] Recently, we reported the total synthesis of kaitocephalin,[3] in which we devised a new methodology to construct the highly substituted pyrrolidine core through a rhodium-catalyzed C–H amination[4,5] followed by an intramolecular nucleophilic attack of a nitrogen atom on a sulfamate group (Scheme 1). Since, to our knowledge, such an approach to heterocyclic compounds has not been reported,[6,7] we became interested in probing the scope and limitations of this particular pyrrolidine synthesis.



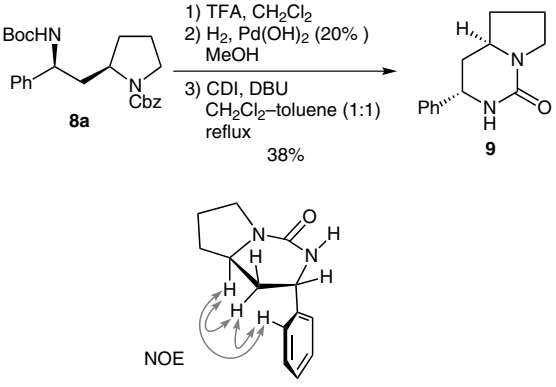
Scheme 1 The key pyrrolidine synthesis

To assess the feasibility of our pyrrolidine synthesis, we first conducted experiments using cyclic *N*-Boc-sulfamate **7a** as a substrate, which was prepared from **4** via **5** and **6a** according to Du Bois' protocol (Scheme 2).[4b] Initially, the cyclization was examined by using NaH (2 equiv) in tetrahydrofuran (THF) according to the conditions employed for the synthesis of **3** (Table 1). In this case, the cyclized compound **8a** was not observed on TLC even after ten hours.



Scheme 2 Preparation of cyclic *N*-Boc-sulfamate **7a**

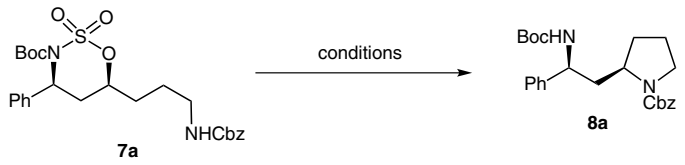
However, when water was added to the mixture, the cyclization occurred instantaneously to give **8a** in 59% yield (Table 1, entry 1). Interestingly, after treatment of **7a** with NaH at 0 °C for 5 min, addition of water (10 equiv) was found to effectively promote the cyclization to afford **8a** in good yield (entry 2). When the reaction was carried out in DMF, **8a** was obtained in high yield[8] and the use of a large excess of water gave comparable results (entries 3 and 4). It turned out that performing the reaction with 3 M NaOH (2 equiv) in place of NaH and H_2O also brought about the cyclization effectively, although the reaction became sluggish (entry 5). However, when a large excess of aqueous NaOH was used, the yield of **8a** decreased markedly (entry 6). MeOH could also be employed in place of water (entry 7), although the use of NaOMe diminished the yield of **8a** (entries 7 and 8). It was also found that no reaction occurred by using K_2CO_3 in MeOH at room tem-



Scheme 3 Confirmation of the stereochemistry of **8a**

SYNLETT 2014, 25, 0133–0137
Advanced online publication: 06.11.2013
DOI: 10.1055/s-0033-1340159; Art ID: ST-2013-U0820-L

Table 1 Base-Promoted Cyclization of **7a**



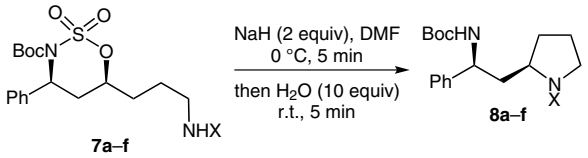
Entry	Conditions	Yield of **8a** (%)[a]
1	NaH (2 equiv), THF, r.t., 10 h	59[b]
2	NaH (2 equiv), THF, 0 °C, 5 min, add H_2O (10 equiv), then r.t., 30 min	78
3	NaH (2 equiv), DMF, 0 °C, 5 min, add H_2O (10 equiv), then r.t., 5 min	99
4	NaH (2 equiv), DMF, 0 °C, 5 min, add H_2O (excess),[c] then r.t., 5 min	92
5	3 M NaOH (2 equiv), DMF, r.t., 2 h	94
6	3 M NaOH (20 equiv), DMF, r.t., 2 h	74
7	NaH (2 equiv), DMF, 0 °C, 5 min, add MeOH (10 equiv), then r.t., 5 min	84
8	NaOMe (2 equiv), MeOH (20 equiv), DMF, r.t., 10 h	55
9	K_2CO_3 (2 equiv), MeOH, r.t., 5 h	no reaction

[a] Isolated yield.
[b] Before aqueous workup, cyclized compound **8a** was not observed on TLC.
[c] H_2O (1 mL) was used for **7a** (0.21 mmol).

perature (entry 9). Although the role of the water is not clear, hydrogen bonding interactions are possibly one of the main factors that influence the reactivity of the process.[9] The NOESY spectrum of **9** prepared from **8a** confirmed the stereostructure of **8a** (Scheme 3), thus proving that the cyclization took place in an S_N2 fashion with complete inversion of the stereochemistry.

We next explored the effect of various protecting groups of the primary amine using the optimized NaH and H_2O conditions (Table 2). As a result, in addition to Cbz, Moc, and Alloc groups, even the sterically demanding Boc group was found to be suitable for this cyclization (entries 1–4). Similarly, benzamide **7e** and acetamide **7f** afforded the corresponding cyclized products **8e** and **8f**, respectively, in comparable yields (entries 5 and 6).

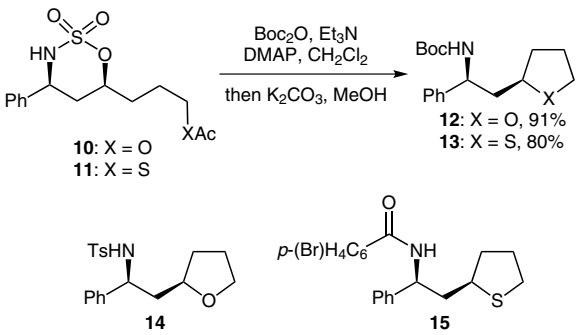
Table 2 Base-Promoted Cyclization of **7a**–**f**



Entry	Sulfamate	X	Pyrrolidine	Yield of **8** (%)[a]
1	**7a**	Cbz	**8a**	99
2	**7b**	Moc	**8b**	89
3	**7c**	Alloc	**8c**	77
4	**7d**	Boc	**8d**	75
5	**7e**	Bz	**8e**	71
6	**7f**	Ac	**8f**	80

[a] Isolated yield.

Based on the optimized reaction conditions, we then evaluated the substrate scope (Table 3). First, five substituted Boc-protected sulfamates **7g–k** were prepared from **6g–k** and subjected to cyclization (Method A). It should be stressed that pyrroidines **8g–j** as well as piperidine **8k** could be synthesized in moderate overall yields regardless of the substitution pattern, even in the case where a quaternary center is present near the reaction site (entries 2–5). Next, step-economical one-pot preparation[10] of **8a** and **8f–k** from **6a** and **6f–k** was also investigated (Method B).[11] Thus, after confirming the formation of **7a** and **7g–k** on TLC, their cyclizations were conducted by adding NaH (3 equiv) followed by water (10 equiv). We were pleased to find that this one-pot procedure worked effectively and, except for **8i**, afforded the corresponding

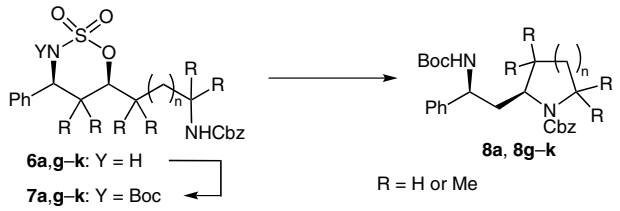


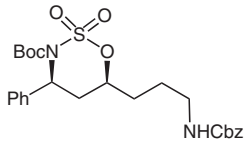
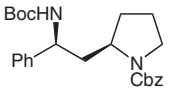
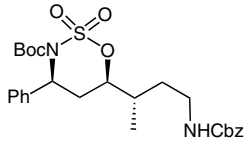
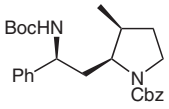
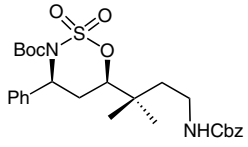
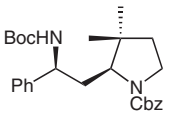
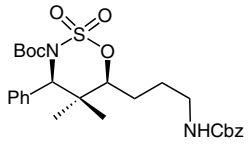
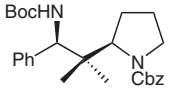
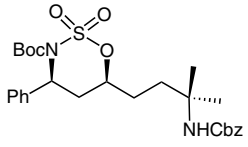
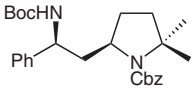
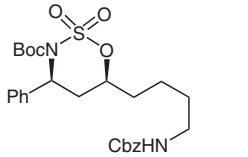
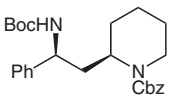
Scheme 4 Synthesis of tetrahydrofuran **12** and tetrahydrothiophene **13**

cyclized products in good yields. In the case of **6i**, butoxycarbonylation did not proceed selectively on the sulfamate nitrogen and the reaction produced several Boc-protected products.

We also examined the synthesis of tetrahydrofuran **12** and tetrahydrothiophene **13** from **10** and **11**, based on the methodology detailed above (Scheme 4). As a result, a one-pot procedure involving butoxycarbonylation of a sulfamate and methanolytic removal of the acetyl group turned out to be operative in these cases, and the cyclized compounds **12** and **13**, respectively, were obtained in good yields. The stereochemistries of **12** and **13** were un-

Table 3 Synthesis of **8a**,**g**–**k**



Entry	Sulfamate	Yield of **7** (%)[a]	Product	Yield of **8** (%)[a]
1	 **7a**	80	 **8a**	99[b] (81)[c]
2	 **7g**	70	 **8g**	84[b] (80)[c]
3	 **7h**	80	 **8h**	79[b] (77)[c]
4	 **7i**	39	 **8i**	74[b] (complex mixture)[c]
5	 **7j**	65	 **8j**	88[b] (77)[c]
6	 **7k**	72	 **8k**	85[b] (80)[c]

[a] Isolated yield.
[b] Method A: (1) Boc_2O, Et_3N-DMAP, CH_2Cl_2; (2) NaH (2 equiv), DMF, 0 °C, 5 min, then H_2O (10 equiv), r.t., 5 min.
[c] Method B (one-pot): Boc_2O, Et_3N-DMAP, DMF, then NaH (3 equiv), 0 °C, 5 min, then H_2O (10 equiv), r.t., 5 min.

ambiguously determined by X-ray crystallographic analysis of their derivatives **14**[12] and **15**.[13]

In conclusion, the present work provides a new methodology for the stereoselective construction of substituted heterocycles such as pyrrolidines, piperidines, tetrahydrofurans, and tetrahydrothiophenes utilizing rhodium-catalyzed C–H amination.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research (A) (22249001) and a Grant-in-Aid for Young Scientists (B) (23790015) from JSPS, a Grant-in-Aid for Scientific Research on Innovative Areas 'Reaction Integration' (No. 2105) (22106538 and 24106736) from MEXT and The Naito Foundation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For recent reviews, see: (a) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3612. (b) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937. (c) Eckert, H. *Molecules* **2012**, *17*, 1074. (d) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (e) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (f) Zhang, M.; Zhang, A.-Q.; Peng, Y. *J. Organomet. Chem.* **2013**, *723*, 224. (g) Ball, C. J.; Willis, M. C. *Eur. J. Org. Chem.* **2013**, 425.

(2) For methodologies for heterocycle synthesis recently developed by our group, see: (a) Takahashi, K.; Haraguchi, N.; Ishihara, J.; Hatakeyama, S. *Synlett* **2008**, 671. (b) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6244. (c) Hatakeyama, S. *Pure Appl. Chem.* **2009**, *81*, 217. (d) Takahashi, K.; Hatakeyama, S. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 951. (e) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*, 5398. (f) Sarkar, S. M.; Taira, Y.; Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2011**, *52*, 923.

(3) Takahashi, K.; Yamaguchi, D.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2012**, *14*, 1644.

(4) (a) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (d) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (e) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

(5) For reviews, see: (a) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347. (b) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758.

(6) For a review on C–H bond functionalization, see: Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.

(7) For heterocycle syntheses utilizing Rh-catalyzed C–H amination, see: (a) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (b) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (c) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926. (d) Conrad, R. M.; Du Bois, J. *Org. Lett.* **2007**, *9*, 5465. (e) Yakura, T.; Yoshimoto, Y.; Ishida, C.; Mabüchi, S. *Tetrahedron* **2007**, *63*, 4429. (f) Narina, S. V.; Kumer, T. S.; George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 65. (g) Yakura, T.; Sato, S.; Yoshimoto, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1284. (h) Kang, S.; Lee, H.-K. *J. Org. Chem.* **2010**, *75*, 237. (i) Tanino, T.; Ichikawa, S.; Shiro, M.; Matsuda, A. *J. Org. Chem.* **2010**, *75*, 1366. (j) Tanino, T.; Ichikawa, S.; Matsuda, A. *Org. Lett.* **2011**, *13*, 4028.

(8) **Preparation of 8a from 4 via 5, 6a, and 7a; Sulfamate 5:** Formic acid (0.69 mL, 15 mmol) was added to neat chlorosulfonyl isocyanate (1.3 mL, 15 mmol) at 0 °C and the mixture was stirred for 5 min. MeCN (10 mL) was added and the mixture was stirred at r.t. for 8 h to generate sulfamoyl chloride (1.5 M in MeCN). To an ice-cooled solution of **4** (1.40 g, 4.28 mmol) in DMA (10 mL) and MeCN (10 mL) was added sulfamoyl chloride (1.5 M in MeCN, 5.7 mL, 8.56 mmol). The mixture was stirred at r.t. for 1 h and saturated $NaHCO_3$ (5 mL) was added at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2 30 g; hexane–EtOAc, 4:1 to 1:1) gave **5** (1.70 g, 97%) as a colorless amorphous solid.
Cyclic Sulfamate 6a: To a solution of **5** (411 mg, 1.08 mmol) in CH_2Cl_2 (10 mL) at r.t. were added MgO (100 mg, 2.50 mmol), $PhI(OAc)_2$ (BAIB; 354 mg, 1.12 mmol), and $Rh_2(OAc)_4$ (9 mg, 0.02 mmol). After stirring at r.t. for 2 h, the mixture was filtered through cotton and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2 30 g; hexane–EtOAc, 3.5:1 to 1.5:1) gave **6a** (371 mg, 84%) as a colorless amorphous solid.
***N*-Boc Sulfamate 7a:** To a stirred solution of **6a** (1.10 g, 0.75 mol) in CH_2Cl_2 (20 mL) at r.t. were added Et_3N (0.59 mL, 4.08 mmol), Boc_2O (712 mg, 0.98 mmol), and DMAP (33 mg, 0.27 mmol). After stirring at r.t. for 5 h, the mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2 15 g; hexane–EtOAc, 4:1) gave **7a** (1.10 g, 80%) as a colorless amorphous solid.
Pyrrolidine 8a: To an ice-cooled solution of **7a** (100 mg, 0.20 mmol) in DMF (2 mL) was added NaH (60% in mineral oil, 16 mg, 0.40 mmol). The mixture was stirred at 0 °C for 5 min, then H_2O (36 μL, 2.0 mmol) was added and the mixture was stirred at r.t. for 5 min. The mixture was neutralized with 1 M HCl, extracted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2 5 g; hexane–EtOAc, 5:1) gave **8a** (83 mg, 99%) as a colorless solid.

(9) For related water-promoted displacement reactions, see: (a) Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649. (b) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (c) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270. (d) Tanaka, Y.; Fuse, S.; Tanaka, H.; Doi, T.; Takahashi, T. *Org. Process Res. Dev.* **2009**, *13*, 1111. (e) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634.

(10) (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (b) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(11) **Representative One-Pot Preparation (Method B):** Et_3N (0.05 mL, 0.38 mmol), DMAP (3 mg, 0.025 mmol), and Boc_2O (72 mg, 0.33 mmol) were added to a solution of **6a** (100 mg, 0.25 mol) in DMF (2 mL) at r.t. The mixture was stirred at r.t. for 5 h, then NaH (60% in mineral oil, 30 mg, 0.75 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 5 min, then H_2O (45 μL, 2.5 mmol) was added, and

the mixture was stirred at r.t. for 5 min. The mixture was neutralized with 1 M HCl, extracted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2 5 g; hexane–EtOAc, 5:1) gave **8a** (85 mg, 81%) as a colorless solid.

(12) The crystallographic data (CCDC 943270) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.
(13) The crystallographic data (CCDC 943271) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.