

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

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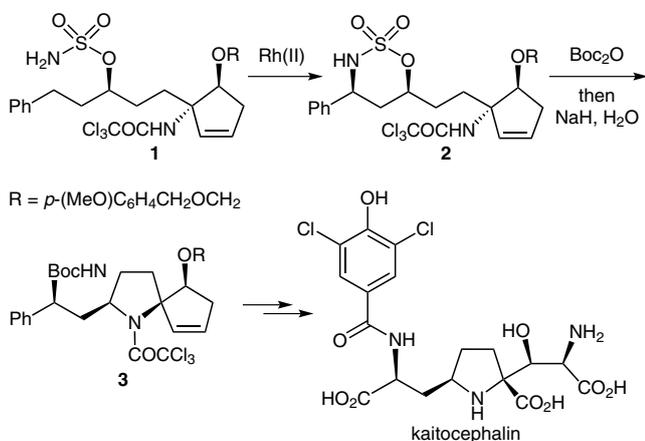
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Abstract: A new stereoselective approach to substituted pyrrolidines and piperidines is described that involves Du Bois' C–H amination reaction, Boc-activation of a cyclic sulfamate group, and base-promoted intramolecular cyclization. This methodology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

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

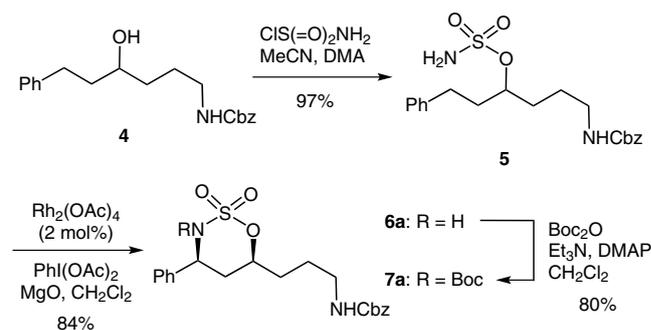
Developing new methodologies for the synthesis of heterocyclic compounds is of great importance in drug discovery, material science, and natural product synthesis.^{1,2} Recently, we reported the total synthesis of kaitocephalin,³ in which we devised a new methodology to construct the highly substituted 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

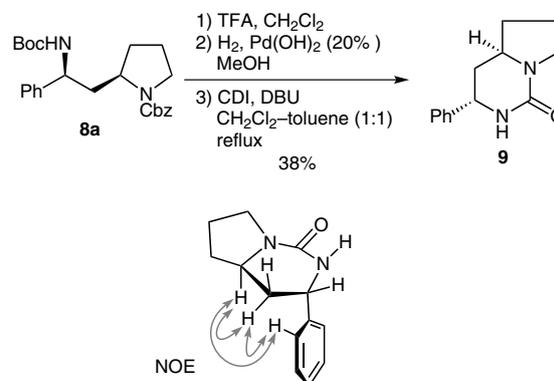
To assess the feasibility of our pyrrolidine synthesis, we first conducted experiments using cyclic *N*-Boc-sulfamate **7a** as a substrate, which was prepared from **4** via **5** and **6a** according to Du Bois' protocol (Scheme 2).^{4b} Initially, the cyclization was examined by using NaH (2 equiv) 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 yield⁸ 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 H₂O 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 K₂CO₃ in MeOH at room tem-



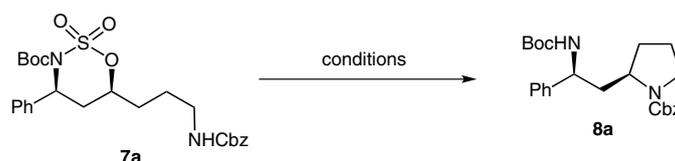
Scheme 3 Confirmation of the stereochemistry of **8a**

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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 ₂ O (10 equiv), then r.t., 30 min	78
3	NaH (2 equiv), DMF, 0 °C, 5 min, add H ₂ O (10 equiv), then r.t., 5 min	99
4	NaH (2 equiv), DMF, 0 °C, 5 min, add H ₂ O (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 ₂ CO 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 H₂O (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 H₂O 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

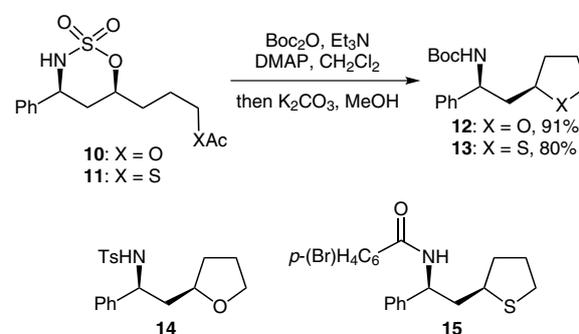
Table 2 Base-Promoted Cyclization of **7a–f**

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.

1–4). Similarly, benzamide **7e** and acetamide **7f** afforded the corresponding cyclized products **8e** and **8f**, respectively, in comparable yields (entries 5 and 6).

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 pyrrolidines **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 preparation¹⁰ 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**

6a,g–k: Y = H
7a,g–k: Y = Boc

8a, 8g–k
R = H or Me

Entry	Sulfamate	Yield of 7 (%) ^a	Product	Yield of 8 (%) ^a
1		80		99 ^b (81) ^c
2		70		84 ^b (80) ^c
3		80		79 ^b (77) ^c
4		39		74 ^b (complex mixture) ^c
5		65		88 ^b (77) ^c
6		72		85 ^b (80) ^c

^a Isolated yield.

^b Method A: (1) Boc₂O, Et₃N-DMAP, CH₂Cl₂; (2) NaH (2 equiv), DMF, 0 °C, 5 min, then H₂O (10 equiv), r.t., 5 min.

^c Method B (one-pot): Boc₂O, Et₃N-DMAP, DMF, then NaH (3 equiv), 0 °C, 5 min, then H₂O (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.

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- 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 NaHCO₃ (5 mL) was added at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over MgSO₄, and concentrated in vacuo. Purification of the residue by column chromatography (SiO₂ 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 CH₂Cl₂ (10 mL) at r.t. were added MgO (100 mg, 2.50 mmol), PhI(OAc)₂ (BAIB; 354 mg, 1.12 mmol), and Rh₂(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 (SiO₂ 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 CH₂Cl₂ (20 mL) at r.t. were added Et₃N (0.59 mL, 4.08 mmol), Boc₂O (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 MgSO₄, and concentrated in vacuo. Purification of the residue by column chromatography (SiO₂ 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 H₂O (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. NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo. Purification of the residue by column chromatography (SiO₂ 5 g; hexane–EtOAc, 5:1) gave **8a** (83 mg, 99%) as a colorless solid.
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- Representative One-Pot Preparation (Method B):** Et₃N (0.05 mL, 0.38 mmol), DMAP (3 mg, 0.025 mmol), and Boc₂O (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 H₂O (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 NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo. Purification of the residue by column chromatography (SiO₂, 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.

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