Concise Synthesis of Bicyclic Aminals by Way of Catalytic Intramolecular C-H Amination and Evaluation of Their Reactivity as Iminium Precursors

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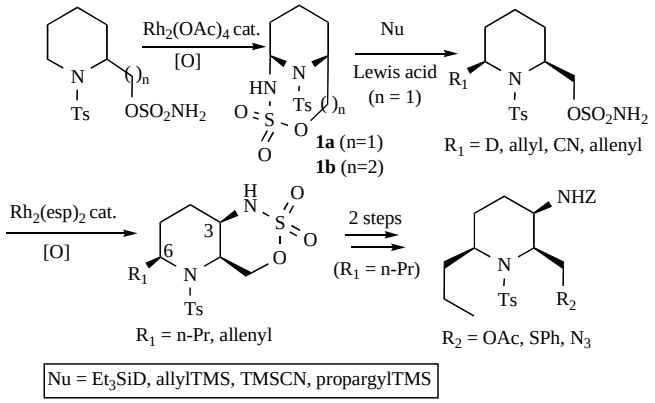
Abstract: The concise synthesis of fused bicyclic aminals by way of intramolecular rhodium-catalyzed C-H amination is reported as well as the evaluation of their reactivity as iminium precursors. In contrast to the well-studied *N,O*-acetal systems, the aminals synthesized were found to be particularly stable under reaction conditions used for nucleophilic addition.

Keywords: C-H amination, aminal, iminium, azacycloalkane, nucleophilic addition.

INTRODUCTION

In less than ten years, the intramolecular-catalyzed amination of unactivated C-H bonds using carbamate or sulfamic ester substrates has established itself as a powerful synthetic tool for the synthesis of valuable nitrogen-containing heterocycles [1]. This process has been used to access directly a diversity of heterocycles, including cyclic sulfamidates, oxazolidine, thiadiazinane and imidazolidinone derivatives, and has been exploited as a key step in the total synthesis of natural products [2, 3]. The strategic advantages of intramolecular C-H amination are numerous; the reaction process is stereospecific and the C-H insertions are generally highly regio- and stereoselective. Guidelines have been formulated to predict the selectivity of the insertion reactions, allowing the rational design of efficient synthetic strategies. The high regioselectivity usually observed is indeed mainly controlled by electronic effects; benzylic, allylic and tertiary C-H bonds as well as sites adjacent to electron-donating groups are generally favored [1]. Amination reactions performed with sulfamate esters lead generally to the formation of the corresponding six-membered ring insertion product. Recently, the synthetic scope of intramolecular-catalyzed C-H amination has been expanded to the synthesis of 7- and 8-membered cyclic sulfamidates through conformational control of reaction regioselectivity [4]. In the piperidine series, this methodology provides access to bicyclic aminals such as **1**, allowing the functionalization of a C-H bond in 1,7- or 1,8-relationship with respect to the activating group (Scheme **1**) [4, 5].



Scheme 1.

Addition of various nucleophiles to the *N*-tosyliminium ion precursor **1a** leads to the stereoselective formation of a new C-C bond at C-6 and regenerates the sulfamic ester that is used again for a second C-H amination at C-3 (Scheme **1**) [5]. Based on this process, a general access to 2,6-disubstituted 3-aminopiperidines was developed. These first results opened the way to unique strategies for the iterative multifunctionalization of unactivated C-H bonds in nitrogen-containing heterocycles. In this process, the sulfamoyloxymethyl group is used several times as a "molecular activating arm" allowing the formation of C-C or C-N bonds [5]. In connection with our studies on iminosugars [6], and to increase the synthetic flexibility of this new concept, we decided to design various synthetic strategies in which the "sulfamoyloxymethyl activating arm" could be involved in the functionalization of more than two saturated methylenes of the azacycloalkane ring. We focused on three systems in the pyrrolidine series (Fig. **1**). In the first one of type **I**, the sulfamoyloxymethyl group is attached to the endocyclic nitrogen with an appropriate linker [7]. This approach may lead to α,α,α,'α'-tetrasubstituted azacycloalkanes by repetitive two-step-reaction (C-H amination followed by nucleophilic ring opening). The two

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other heterocyclic systems are pyrrolidines substituted at C-3 by a sulfamoyloxy or a sulfamoyloxymethyl group (type **II** and **III** respectively). It was expected that the application of our iterative strategy to these substrates could lead to the formation of a new C-N bond at C-4 and of new C-C bonds at C-2 and C-5.

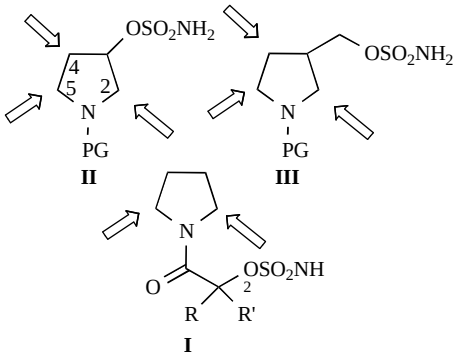


Fig. (1).

Starting from these three heterocyclic systems, a study was performed to investigate the regio- and diastereoselectivity of the two key steps of the process: the C-H amination reaction and the nucleophilic addition to aminals. It is noteworthy that, in contrast to nucleophilic addition to *N,O*-acetals [8], the reaction of aminals with nucleophiles in the presence of Lewis acids has been almost unexplored [9]. To our knowledge, there were no reactions of this type reported with cyclic aminals before we started our first study in the piperidine series [4, 5]. Herein, we wish to report our findings in the feasibility of the iterative multifunctionalization process.

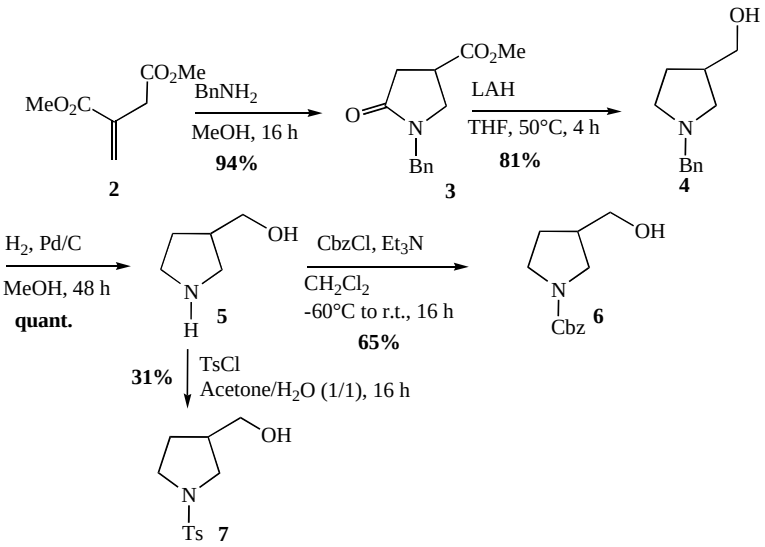
RESULTS AND DISCUSSION

Synthesis of Test Substrates

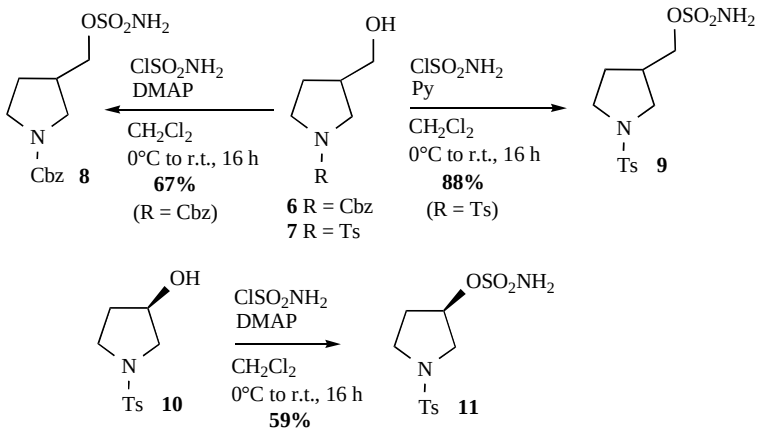
Pyrrolidines of type **III** required the longest synthetic sequence (Scheme **2**). The synthesis began with the conjugate Michael addition of benzylamine to itaconic acid dimethyl ester (**2**), followed by spontaneous cyclization to afford in high yield the expected lactam **3** [10]. Reduction of the lactam and ester carbonyl groups with LAH gave the *N*-benzyl-3-hydroxylmethyl pyrrolidine (**4**) [11]. In order to evaluate the influence of the endocyclic nitrogen protecting group on the outcome of the two key reactions of our process, the *N*-Tosyl and *N*-carbobenzoxy (*N*-Cbz) analogs of **4** were prepared following a two-step sequence. Removal of the *N*-benzyl group of compound **4** under classical hydrogenolysis conditions provided 3-hydroxylmethyl pyrrolidine (**5**) in quantitative yield. Reaction of **5** with CbzCl in the presence of triethylamine afforded the expected *N*-Cbz protected pyrrolidine **6** in acceptable yield. In contrast, the chemoselective protection [12] of the endocyclic amine with a tosyl group in the presence of a primary hydroxyl group proved difficult. The desired *N*-tosyl pyrrolidine **7** could be obtained in only 31% yield by treatment of **5** with 1.1 equiv. of TsCl in 50% aqueous acetone [12]. Attempts to optimize this process led to the formation of significant amount of the di-tosyl analog of **7**. Alcohols **6** and **7** were then reacted with sulfamoyl chloride and pyridine or DMAP [13] in dichloromethane to afford the expected test substrates **8** and **9** of type **III** in good yields (Scheme **3**).

Sulfamoylation of alcohol **4** under these conditions was found to be unsuccessful probably because of the reactivity of the endocyclic amino group. Pyrrolidine **11** of type **II** was prepared following the same sulfamoylation procedure from the commercially available enantiopure 3-(*R*)-hydroxy-pyrrolidine **10**.

Based on our recent work on the amination of α-amino C-H bonds in azacycloalkanes with the sulfamoyloxy group attached to the endocyclic nitrogen atom [7], we selected sulfamate **14** as test substrate of type **I** (Scheme **4**). This previous study has indeed demonstrated the decisive influence of ring-size and *gem*-dialkyl effect on α-amino C-H insertion, the best results being obtained in the pyrrolidine series. Cyclopropyl-containing pyrrolidine **14** was prepared following a 2-step synthesis [7]. The coupling of pyrrolidine to unprotected β-hydroxy carboxylic acid **13** using HOBt

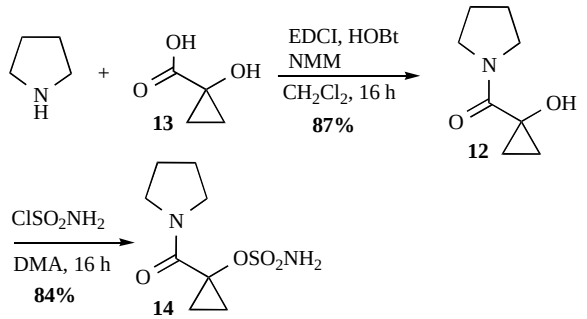


Scheme 2.



Scheme 3.

and EDCI produced the expected amide **12** in 87% yield (Scheme **4**) [14]. The second sulfamoylation step turned out to be more challenging as tertiary sulfamic esters are known to be intrinsically unstable because of the activating nature of the sulfamoyl group for elimination and/or nucleophilic displacement [1a,b]. The best conditions found were obtained by using *N*,*N*-dimethylacetamide (DMA) as the solvent, without pyridine, according to the method [15] described by the group of Okada for primary and secondary alcohols. The process was applied successfully to tertiary alcohol **12** to provide sulfamate **14** in 84% yield (Scheme **4**).



Scheme 4.

C-H Amination Reactions

Having test substrates **8**, **9**, **11** and **14** in hand, we investigated the C-H amination reaction, the first key step of the iterative process. Following a standard protocol using $PhI(OAc)_2$ (1.1 eq.), MgO (2.3 eq.) and 5 mol% of $Rh_2(OAc)_4$ [4], pyrrolidine **14** was converted into the aminal **15** in an excellent yield of 86% (Table **1**, entry 1). The yield of the reaction was not improved by using $Rh_2(esp)_2$, an efficient C-H amination catalyst (entry 2) [16].

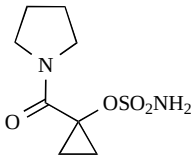
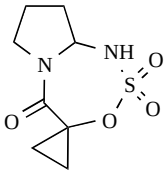
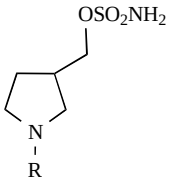
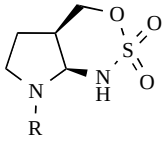
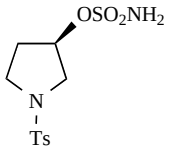
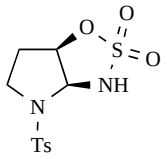
Pyrrolidines of type **III** were also found to be good substrates for intramolecular-catalyzed C-H amination. The conversion was complete after few hours and the bicyclic aminals **16** and **17** were obtained in high yields (entries 3-4). The amination at C-2 is indeed favored by the formation of a six-membered ring and by the favorable presence of a nitrogen atom in α-position. The highly favored formation of the oxathiazinane ring may be rationalized by the elongated S-N and S-O bond length and the obtuse N-S-O angle of the sulfamate (~ 103°), which match the metrical parameters of the 6-membered sulfamidate (~ 105°) [1a,b]. The formation of the oxathiazolidine ring would require an unfavorable compression of this angle to 95°. Pyrrolidine **11** was a more challenging substrate in terms of regioselectivity. The two secondary C-H bonds at C-2 and C-5 are both activated by the presence of a *N*-tosyl group; the amination of the C-5 position may be facilitated by the formation of a six-membered ring but disfavored by the ring-strain of the bridged bicyclic system thus generated. Insertion into the C-H bond at C-2 may lead to a less favored 5-membered ring. Nevertheless, the reaction was found to be highly regioselective; under typical amination conditions, the bicyclic aminal **18** corresponding to the insertion into the C-H bond at C-2, was obtained in 95% yield (entry 5).

Evaluation of Bicyclic Aminals as Iminium Precursors

Our iterative strategy required reactions of nucleophiles with the bicyclic aminals synthesized. However, while nucleophilic addition to *N*,*O*-acetals had been widely described [8], there were only few reported reactions with aminals in the presence of Lewis acids [9]. Furthermore, before our first study with piperidines **1** [4, 5], there were no reactions of this type reported with cyclic aminals. To evaluate the synthetic scope of this reaction, a systematic study was first performed with aminals **16**-**17**. Quite unexpectedly, the optimized conditions developed for aminal **1a** [5] failed to afford the expected addition product; treatment of aminal **17** with 4 equivalents of allylsilane and $BF_3.OEt_2$ or $SnCl_4$ led to no conversion. The same disappointing results were obtained with aminal **16** protected with a *N*-Cbz group. The reaction of aminal **17** with 6 equiv. of TMSCN in the presence of 1 equiv. of $SnCl_4$ gave better results. The desired 2-carbonitrile pyrrolidine **19** could be obtained in 20% yield and good diastereoselectivity in favor of the 2,3-cis derivative. The relative configuration of the substituents in pyrrolidine **19** were unambiguously established by the ^1H NMR spectra (COSY and NOESY). The addition of more equivalents of Lewis acid was found to increase the reaction yield to 39% (Scheme **5**).

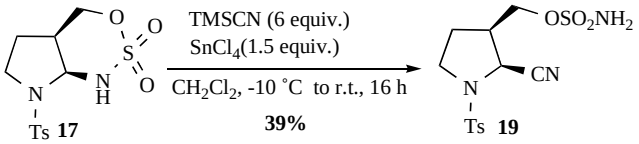
The *N*-carbobenzoxy (*N*-Cbz) analog of **17**, compound **16** failed to react under these conditions. Some conversion was observed when the reaction was performed with the

Table 1. Intramolecular C-H Amination of Sulfamic Esters[a]

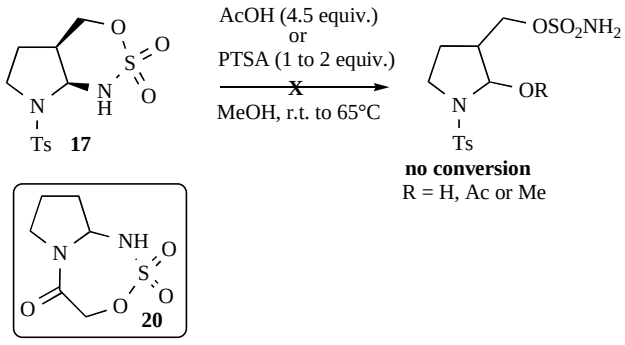
Entry	Substrate	Product	Reaction time	Yield[c]
1(**14**)[b] 2(**14**)[b]		 **15**	16h 16h	86% 83%[d]
3(**8**)[b] 4(**9**)[b]		 **16** (R=Cbz) **17** (R=Ts)	3h 2h	86% 83%[e]
5(**11**)[b]		 **18**	1.5h	95%

[a]Reaction conditions: CH_2Cl_2, 40 °C, substrate: $PhI(OAc)_2$: MgO:$Rh_2(OAc)_4$ 1:1.1:2.3:0.05. [b]Amination substrate. [c]Isolated yield after purification by flash chromatography on silica gel. [d]$Rh_2(esp)_2$ was used instead of $Rh_2(OAc)_4$. [e]62% isolated yield after purification by recrystallization.

more strained bicyclic aminal **18**. However, no trace amount of the desired addition product could be detected by ^1H NMR or mass spectral analysis on the crude reaction mixture. To overcome the very low reactivity of aminals **16**-**18**, we decided to convert them to the corresponding hemi-aminals by treatment with a Brönsted acid in MeOH. Reaction of **17** with 1 to 2 equiv. of *p*-toluenesulfonic acid in MeOH at various temperatures led to no conversion of the starting material (Scheme **6**) [17].



Scheme 5.



Scheme 6.

Treatment of **17** or **18** with acetic acid in MeOH at 65°C was then performed as these conditions have previously been found to open 2-benzyl-8-tosyl-2,8-diazabicyclo[2.2.0] octane ring system [18]. Again no conversion was observed with **17** or **18** under these conditions. The reactivity of bicyclic aminal **15** and its close analog **20** [7] (Scheme **6**) was then explored with TMSCN or allylsilane by treatment with 0.2 equiv. to 1.2 equiv. of various Lewis acids ($BF_3.OEt_2$, $SnCl_4$, $TiCl_4$ or $Sc(OTf)_3$). Again, these aminals were found to be particularly unreactive. As observed for aminal **17**, attempts to convert **15** into the corresponding hemi-aminal by treatment with MeOH in the presence of *p*-toluenesulfonic acid or $BF_3.OEt_2$ failed. Comparison of our results and those reported in the literature indicated clearly that if acyclic [9d] or monocyclic aminals (e.g. 2-amino 1-azacycloalkanes) [9a-c] are readily opened by nucleophiles under acidic conditions, bicyclic aminal substrates are much more challenging.

EXPERIMENTAL

General Methods

Dichloromethane (CH_2Cl_2) was distilled over CaH_2 under Ar. All reactions requiring anhydrous conditions were carried out under Ar. Column chromatography: silica gel 60 (70-230 mesh, 0.063-0.200 mm) was purchased from E. Merck. Thin Layer Chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F_{254} purchased from E. Merck. IR spectra (cm^{-1}) were recorded on a Perkin–Elmer Spectrum One Spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX250, AC 300 or AC 400 with solvent peaks as reference. The ^1H signals were assigned by 2D experiments (COSY). ESI-HRMS mass spectra were carried out on a Bruker MicroTOF spectrometer. Specific rotations were determined at room

temperature (20°C) in a Perkin–Elmer 241 polarimeter for sodium (λ = 589 nm).

General O-Sulfamoylation Procedure

To a 60 mM solution of alcohol derivative in dichloromethane were added pyridine or DMAP (2 eq.) and sulfamoyl chloride (2 eq.) at 0 ºC. The mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of water. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the crude product, which was purified by flash chromatography.

General Intramolecular C-H Amination Procedure

To a 40 mM solution of sulfamate ester derivative dissolved in degassed dichloromethane were successively added MgO (2.3 eq.), $PhI(OAc)_2$ (1.1 eq.) and $Rh_2(OAc)_4$ (0.05 eq.). The mixture was stirred at 40 ºC until TLC indicated the total conversion of starting material. After cooling to room temperature, the solution was filtered through a pad of celite which was washed three times with dichloromethane. The filtrate was evaporated under reduced pressure. The crude mixture was purified by chromatography on silica gel.

(±)-N-Carbobenzoxy-3-hydroxymethylpyrrolidine (6)

To a suspension of (±)-3-hydroxymethylpyrrolidine (**5**) (903 mg, 8.92 mmol) and Et_3N (3.1 mL, 22.2 mmol) in dichloromethane (8 mL) at -60 ºC, was added dropwise a solution of benzyl chloroformate (1.3 mL, 8.92 mmol) in dichloromethane (3 mL). The reaction mixture was warmed slowly to room temperature and stirred for 16 h. 15 ml of 1M HCl was then added slowly. The organic layer was separated and the aqueous layer extracted twice with dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to give the crude product, which was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to give **6** as a colorless oil (1.36 g, 65%); ν_{max} (neat) 3640–3130 (br), 1674, 1418, 1357, 1122, 1078 cm^{-1}; ^1H NMR (400 MHz, 353 K, DMSO-d_6) δ7.37–7.26 (5H, m, Ph), 5.08 (2H, s, PhC*H*$_2$), 4.30 (1H, bt, *J* 5.2 Hz, OH), 3.45 (1H, dd, *J* 10.8, 7.6 Hz, OC*H*a), 3.42–3.35 (3H, m, H-2a, H-5a, OC*H*b), 3.31 (1H, dt, *J* 10.8, 7.6 Hz, H-5b), 3.12 (1H, dd, *J* 10.4, 6.8 Hz, H-2b), 2.36–2.26 (1H, m, H-3), 1.95–1.87 (1H, m, H-4a), 1.64 (1H, dq, *J* 15.6, 7.6 Hz, H-4b); ^{13}C NMR (100.6 MHz, 353 K, DMSO-d_6) δ153.6, 136.9, 127.7, 127.0, 126.8, 65.2, 62.1, 48.1, 44.8, 39.7, 26.8; *m/z* (ESI) 258.1 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 258.108. $C_{13}H_{17}NNaO_3$ requires 258.110.

(±)-3-Hydroxymethyl-N-(toluene-4-sulfonyl)pyrrolidine (7)

To a solution of **5** (102 mg, 1.01 mmol) in 50% aqueous acetone (5 mL) was added *p*-toluenesulfonyl chloride (212 mg, 1.11 mmol). The reaction mixture was stirred for 16 h at room temperature. Acetone was evaporated and the resulting solution extracted twice with ethyl acetate. The combined organic layer was washed once with water, dried over $MgSO_4$, filtered and the solvent evaporated to give pure **7** as a colorless oil (79 mg, 31%); ν_{max} (neat) 3650–3130 (br), 1331, 1155, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDC1_3$) δ7.62, 7.25 (4H, 2d, *J* 8.1, *p*-Tol), 3.39 (1H, dd, *J* 10.5, 6.3 Hz, OC*H*a), 3.32 (1H, dd, *J* 10.5, 7.2 Hz, OC*H*b), 3.25–3.19 (1H, buried m, H-5a), 3.24 (1H, dd, *J* 10.2, 7.5 Hz, H-2a), 3.08 (1H, dt, *J* 9.6, 7.5 Hz, H-5b), 2.98 (1H, dd, *J* 10.2, 6.3 Hz, H-2b), 2.56 (1H, bs, OH), 2.35 (3H, s, CH_3), 2.30–2.15 (1H, m, H-3), 1.85–1.75 (1H, m, H-4a), 1.54–1.43 (1H, m, H-4b); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ143.6, 133.3, 129.4, 127.6, 63.9, 50.4, 47.4, 40.7, 27.5, 21.5; *m/z* (ESI) 278.1 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 278.083. $C_{12}H_{17}NNaO_3S$ requires 278.082.

(±)-N-Carbobenzoxy-3-sulfamoyloxymethylpyrrolidine (8)

Compound **6** (1.10 g, 4.67 mmol) was treated as described in the general *O*-sulfamoylation procedure using DMAP (1.14 g, 9.33 mmol) and sulfamoyl chloride (1.35g, 9.33 mmol). The crude product was purified by flash chromatography (EtOAc) to give **8** as a colorless oil (0.98 g, 67%); ν_{max} (neat) 3440–2990 (br), 1672, 1429, 1358, 1176, 1115 cm^{-1}; ^1H NMR (400 MHz, 353 K, DMSO-d_6) δ7.37–7.30 (5H, m, Ph), 7.16 (2H, bs, NH_2), 5.09 (2H, s, PhC*H*$_2$), 4.07 (1H, dd, *J* 10.0, 6.4 Hz, OC*H*a), 4.02 (1H, dd, *J* 10.0, 7.2 Hz, OC*H*b), 3.53 (1H, dd, *J* 10.8, 7.6 Hz, H-2a), 3.49–3.41 (1H, m, H-5a), 3.34 (1H, dd, *J* 10.4, 7.6 Hz, H-5b), 3.16 (1H, dd, *J* 10.8, 6.8 Hz, H-2b), 2.66–2.55 (1H, m, H-3), 2.05–1.97 (1H, m, H-4a), 1.71 (1H, dq, *J* 15.6, 7.6 Hz, H-4b); ^{13}C NMR (100.6 MHz, 353 K, DMSO-d_6) δ153.5, 136.7, 127.7, 127.1, 126.8, 69.5, 65.3, 47.7, 44.5, 36.8, 26.7; *m/z* (ESI) 337.1 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 337.082. $C_{13}H_{18}N_2NaO_5S$ requires 337.083.

(±)-3-sulfamoyloxymethyl-N-(toluene-4-sulfonyl)pyrrolidine (9)

Compound **7** (793 mg, 2.89 mmol) was treated as described in the general *O*-sulfamoylation procedure using pyridine (0.46 mL, 5.80 mmol) and sulfamoyl chloride (670 mg, 5.80 mmol). The crude product was purified by flash chromatography (1:1 → 2:1 EtOAc/Pet. Ether) to give **9** as a white solid (850 mg, 88%); ν_{max} (neat) 3389, 3294, 1334, 1192, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDC1_3$) δ7.67, 7.31 (4H, 2d, *J* 8.1, *p*-Tol), 5.31 (2H, bs, NH_2), 4.04 (1H, dd, *J* 9.9, 6.3 Hz, OC*H*a), 3.97 (1H, dd, *J* 9.9, 7.8 Hz, OC*H*b), 3.38–3.30 (1H, m, H-5a), 3.27 (1H, dd, *J* 10.2, 7.5 Hz, H-2a), 3.12 (1H, dt, *J* 10.2, 5.7 Hz, H-5b), 3.08 (1H, dd, *J* 10.2, 7.8 Hz, H-2b), 2.58–2.42 (1H, m, H-3), 2.40 (3H, s, CH_3), 1.97–1.85 (1H, m, H-4a), 1.66–1.54 (1H, m, H-4b); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.1, 132.8, 130.0, 127.7, 71.2, 50.2, 47.3, 37.6, 27.4, 21.6; *m/z* (ESI) 357.1 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 357.053. $C_{12}H_{18}N_2NaO_5S_2$ requires 357.055.

(R)-3-sulfamoyloxy- N-(toluene-4-sulfonyl)pyrrolidine (11)

(*R*)-3-Hydroxy-*N*-(toluene-4-sulfonyl)pyrrolidine (500 mg, 2.08 mmol) was treated as described in the general *O*-sulfamoylation procedure using DMAP (506 mg, 4.14 mmol) and sulfamoyl chloride (478 mg, 4.14 mmol). The crude product was purified by flash chromatography (2:1 EtOAc/Pet. Ether) to give **11** as a white solid (390 mg, 59%); $[\alpha]_D^{20}$-1.5 (*c* 1.0, Acetone); ν_{max} (neat) 3329, 3234, 1376, 1334, 1173, 1152 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6) δ7.73, 7.44 (4H, 2d, *J* 8.1, *p*-Tol), 6.74 (2H, bs, NH_2), 5.10–5.06 (1H, m, H-3), 3.55 (1H, dd, *J* 11.7, 2.1 Hz, H-2a),

3.48 (1H, dd, *J* 11.7, 4.2 Hz, H-2b), 3.39–3.32 (1H, m, H-5a), 3.28 (1H, dt, *J* 9.6, 7.8 Hz, H-5b), 2.43 (3H, s, CH_3), 2.14–2.09 (2H, m, H-4); ^{13}C NMR (75.5 MHz, Acetone-d_6) δ144.6, 134.8, 130.6, 128.5, 80.0, 54.5, 46.7, 32.6, 21.4; *m/z* (ESI) 343.0 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 343.036. $C_{11}H_{16}N_2NaO_5S_2$ requires 343.039.

N-[1-(Hydroxycyclopropyl)-carbonyl]-pyrrolidine (12)

To a solution of carboxylic acid **13** (1.0 g, 9.80 mmol) in dichloromethane (25 mL), were added pyrrolidine (650 µL, 7.79 mmol), HOBt (1.16 g, 8.58 mmol), *N*-methylmorpholine (1.8 mL, 16.37 mmol), and EDCI (2.24 g, 11.7 mmol) at room temperature. The solution was stirred for 16 h. The reaction was quenched with a solution of saturated NH_4Cl and diluted with water and dichloromethane. The mixture was extracted with dichloromethane three times. The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated. The resulting residue was purified by flash chromatography (95:5 CH_2Cl_2/Acetone) to yield **12** as a solid (1.05 g, 87%); ^{1}H NMR (400 MHz, Acetone-d_6) δ5.16 (1H, s, OH), 3.85-3.77 (2H, m, H-2), 3.38-3.30 (2H, m, H-5), 1.92-1.84 (2H, m, H-3), 1.84-1.76 (2H, m, H-4), 1.25-1.17 (2H, m, CH cyclopropyl), 0.83-0.75 (2H, m, CH cyclopropyl); ^{13}C NMR (62.9 MHz, Acetone-d_6) δ171.2, 56.6, 47.6, 47.3, 27.0, 24.2, 14.7.

N-[1-(Sufamoyloxycyclopropyl)-carbonyl]-pyrrolidine (14)

To a solution of **12** (1.05 g, 6.77 mmol) in *N*,*N*-dimethylacetamide (11 mL), was added sulfamoyl chloride (2.33 g, 20.17 mmol) at 0 ºC. The reaction was stirred at room temperature for 16 h. To the reaction mixture was added water and ethyl acetate. The organic layer was separated and the aqueous layer extracted twice with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (99:1 → 90:10 CH_2Cl_2/Acetone) to afford **14** as a solid (1.34 g, 84%); ν_{max} (neat) 3406, 1633, 1462, 1373, 1136 cm^{-1}; ^{1}H NMR (400 MHz, Acetone-d_6) δ6.93 (2H, s, NH_2), 3.72 (2H, t, *J* 6.4 Hz, H-2), 3.36 (2H, t, *J* 6.8 Hz, H-5), 1.95-1.87 (2H, m, H-3), 1.85-1.77 (2H, m, H-4), 1.41-1.33 (2H, m, CH cyclopropyl), 1.28-1.20 (2H, m, CH cyclopropyl); ^{13}C NMR (62.9 MHz, Acetone-d_6) δ166.4, 63.3, 47.3, 47.2, 26.7, 24.1, 11.7; *m/z* (ESI) 257.5 $[M+Na]^+$, 235.0 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$, found 257.057. $C_8H_{14}N_2NaO_4S$ requires 257.057.

(±)-Spiro[cyclopropane-1,4'(5'H)-[1H]pyrrolo[2,1-d][1,2,3,5]oxathiadiazepin]-5'-one, tetrahydro-2',2-dioxide (15)

Compound **14** (270 mg, 1.15 mmol) was treated during 16 h as described in the general intramolecular C-H amination procedure using MgO (107 mg, 2.65 mmol), $PhI(OAc)_2$ (420 mg, 1.30 mmol) and $Rh_2(OAc)_4$ (25 mg, 57 µmol). The crude mixture was purified by flash chromatography (2:8 CH_3CN/CH_2Cl_2) to give **15** as a solid (230 mg, 86%); ν_{max} (neat) 3442, 1628, 1466, 1373, 1192, 1148 cm^{-1}; ^{1}H NMR (400 MHz, Acetone-d_6) δ8.06 (1H, s, NH), 5.47 (1H, t, *J* 6.0 Hz, H-2), 3.55-3.46 (2H, m, H-5), 2.43-2.35 (1H, m, H-3a), 2.02-1.85 (3H, m, H-3b, H-4), 1.60-1.47 (2H, m, CH cyclopropyl), 1.37-1.27 (2H, m, CH cyclopropyl); ^{13}C NMR (62.9 MHz, Acetone-d_6) δ166.8, 68.5, 64.1, 48.0, 33.5, 21.7, 15.6, 14.8; *m/z* (ESI) 255.5 $[M+Na]^+$, 233.5 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$, found 255.041. $C_8H_{12}N_2NaO_4S$ requires 255.042.

(±)-(1R*, 6R*)-2,9-Diaza-9-carbobenzoxy-4-oxa-3-thia-bicyclo[4.3.0]nonane-3,3-dioxide (16)

Compound **8** (722 mg, 2.30 mmol) was treated during 3 h as described in the general intramolecular C-H amination procedure using MgO (213 mg, 5.29 mmol), $PhI(OAc)_2$ (815 mg, 2.53 mmol) and $Rh_2(OAc)_4$ (51 mg, 0.12 mmol). The crude mixture was purified by flash chromatography (1:1 → 2:1 EtOAc/Pet. Ether) to give **16** as a white crystalline solid (618 mg, 86%); ν_{max} (neat) 3160, 1690, 1424, 1350, 1190 cm^{-1}; ^{1}H NMR (400 MHz, 353 K, DMSO-d_6) δ7.52 (1H, bs, NH), 7.40–7.31 (5H, m, Ph), 5.35 (1H, bd, *J* 4.8 Hz, H-1), 5.17 (1H, d, *J* 12.8 Hz, PhC*H*a), 5.13 (1H, d, *J* 12.8 Hz, PhC*H*b), 4.70 (1H, dd, *J* 12.0, 3.6 Hz, H-5a), 4.46 (1H, dd, *J* 12.0, 1.6 Hz, H-5b), 3.53 (1H, td, *J* 10.4, 2.4 Hz, H-8a), 3.38 (1H, dt, *J* 10.4, 8.0 Hz, H-8b), 2.42–2.33 (1H, m, H-6), 2.24–2.13 (1H, m, H-7a), 2.06–1.99 (1H, m, H-7b); ^{13}C NMR (100.6 MHz, 353 K, DMSO-d_6) δ152.7, 136.2, 127.7, 127.2, 126.8, 69.6, 69.5, 65.8, 44.5, 34.5, 23.2; *m/z* (ESI) 335.1 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 335.066. $C_{13}H_{16}N_2NaO_5S$ requires 355.067.

(±)-(1R*, 6R*)-2,9-Diaza-4-oxa-3-thia-9-(toluene-4-sulfonyl)-bicyclo[4.3.0]nonane-3,3-dioxide (17)

Compound **9** (100 mg, 0.30 mmol) was treated during 2 h as described in the general intramolecular C-H amination procedure using MgO (28 mg, 0.69 mmol), $PhI(OAc)_2$ (106 mg, 0.33 mmol) and $Rh_2(OAc)_4$ (7 mg, 15 µmol). The crude mixture was purified by flash chromatography (1:1 EtOAc/Pet. Ether) to give **17** as a white crystalline solid (82 mg, 83%). As an alternative to flash chromatography, the compound may be purified by recrystallisation from hot methanol (62% yield); ν_{max} (neat) 3207, 1426, 1335, 1189, 1161 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.86 (1H, d, *J* 7.5 Hz, NH), 7.75, 7.44 (4H, 2d, *J* 8.1, *p*-Tol), 5.22 (1H, dd, *J* 7.5, 4.5 Hz, H-1), 4.58 (1H, dd, *J* 12.3, 3.3 Hz, H-5a), 4.15 (1H, d, *J* 12.3 Hz, H-5b), 3.40 (1H, t, *J* 9.3 Hz, H-8a), 3.09 (1H, dt, *J* 9.3, 7.5 Hz, H-8b), 2.40 (3H, s, CH_3), 2.22–2.09 (1H, m, H-7a), 1.98–1.80 (2H, m, H-6, H-7b); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ143.7, 134.9, 129.9, 127.2, 71.9, 69.6, 46.5, 35.1, 23.9, 21.0; *m/z* (ESI) 355.0 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 355.035. $C_{12}H_{16}N_2NaO_5S_2$ requires 355.039.

(1R, 5R)-4,6-Diaza-2-oxa-3-thia-6-(toluene-4-sulfonyl)-bicyclo[3.3.0]octane-3,3-dioxide (18)

Compound **11** (364 mg, 1.14 mmol) was treated during 1.5 h as described in the general intramolecular C-H amination procedure using MgO (105 mg, 2.61 mmol), $PhI(OAc)_2$ (403 mg, 1.25 mmol) and $Rh_2(OAc)_4$ (25 mg, 57 µmol). The crude mixture was purified by flash chromatography (2:1 EtOAc/Pet. Ether) to give **18** as a white solid (346 mg, 95%); $[\alpha]_D^{20}$-107.5 (*c* 1.0, Acetone); ν_{max} (neat) 3234, 1337, 1195, 1154 cm^{-1}; ^{1}H NMR (300 MHz, Acetone-d_6) δ7.81 (2H, d, *J* 8.1, *p*-Tol), 7.72 (1H, bd, *J* 5.4 Hz, NH), 7.42 (2H, d, *J* 8.1, *p*-Tol), 5.95 (1H, bt, *J* 5.4 Hz, H-5), 5.51 (1H, t, *J* 5.4 Hz, H-1), 3.65 (1H, ddd, *J* 10.5, 8.1, 1.5 Hz, H-7a), 3.48 (1H, td, *J* 10.5, 5.7 Hz, H-7b), 2.43 (3H, s, CH_3), 2.22 (1H, bdd, *J* 14.4, 5.7 Hz, H-8a), 2.17–2.08 (1H, m, H-8b); ^{13}C NMR (75.5 MHz, Acetone-d_6) δ144.8, 137.4,

130.6, 128.3, 86.4, 75.2, 46.4, 31.7, 21.4; *m/z* (ESI) 341.0 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 341.023. $C_{11}H_{14}N_2NaO_5S_2$ requires 341.024.

(±)-(2S, 3R*)-2-cyano-3-sulfamoyloxymethyl-N-(toluene-4-sulfonyl)pyrrolidine (19)*

To a solution of **17** (50 mg, 0.15 mmol) and TMSCN (0.12 mL, 0.90 mmol) in dichloromethane (1.5 mL), was added $SnCl_4$ 1M solution in dichloromethane (0.22 mL) at -10 ºC. The reaction mixture was warmed slowly to room temperature and stirred for 16 h. The reaction mixture was then diluted with dichloromethane, neutralized to pH 7 with saturated $NaHCO_3$ and the biphasic mixture filtered through a pad of celite. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to give the crude product, which was purified by flash chromatography (2:1 EtOAc/Pet. Ether) to give **19** as a colorless oil (21 mg, 39%, 78% d.e. in favor of the cis isomer); ν_{max} (neat) 3379, 2249, 1345, 1159 cm^{-1}; Major (cis) isomer: ^1H NMR (300 MHz, $CDC1_3$) δ7.75, 7.35 (4H, 2d, *J* 8.4, *p*-Tol), 4.80 (1H, d, *J* 7.5 Hz, H-2), 4.38 (1H, dd, *J* 9.9, 5.4 Hz, OC*H*a), 4.25 (1H, t, *J* 9.9 Hz, OC*H*b), 3.49 (1H, td, *J* 9.6, 1.8 Hz, H-5a), 3.34 (1H, dt, *J* 9.6, 7.2 Hz, H-5b), 2.78–2.63 (1H, m, H-3), 2.42 (3H, s, CH_3), 2.18–2.06 (1H, m, H-4a), 1.89–1.70 (1H, m, H-4b); Major (cis) isomer ^{13}C NMR (75.5 MHz, $CDCl_3$) δ144.9, 133.7, 130.2, 127.6, 115.5, 68.7, 51.7, 46.7, 41.7, 26.8, 21.6; *m/z* (ESI) 382.1 $[M+Na]^+$, 333.1 $[M-CN]^+$; HRMS (ESI): $[M+Na]^+$, found 382.054. $C_{13}H_{17}N_3NaO_5S_2$ requires 382.050. NOE effect observed between H-2 and H-3.

CONCLUSION

In conclusion, our work demonstrates the interest of intramolecular C-H amination for the concise and efficient synthesis of bicyclic aminals. However, the second key step of our iterative strategy has been mostly unsuccessful to date due to the rather unexpected absence of reactivity of these systems. In contrast to bridged bicyclic aminal **1a** [5] or to well-studied hemi-aminals [8], the fused bicyclic aminals evaluated were generally stable under classical reaction conditions used for nucleophilic addition. While it has not yet been possible to obtain the desired addition products in good yields, our study provides useful insights into the reactivity trends of bicyclic aminals.

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