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Brønsted Acid-Catalyzed Intramolecular Hydroamination of Protected Alkenylamines. Synthesis of Pyrrolidines and Piperidines

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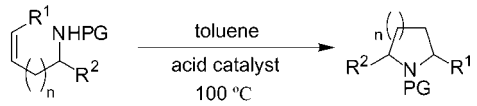
ABSTRACT



The cyclization of aminoalkenes bearing an electron-withdrawing group on the nitrogen atom was catalyzed by triflic or sulfuric acid in toluene. Pyrrolidines and piperidines were formed in excellent yields. *N*-Phenylanilides also underwent cyclization to form γ-lactams.

Nitrogen-containing saturated heterocyclic systems are important core structures in organic chemistry because of their presence in many natural products. For this reason simple procedures for the formation of pyrrolidines and piperidines are highly desirable.[1] One of the most appealing approaches to these heterocycles is hydroamination, in which the nitrogen carbon bond is formed by the addition of an amine to an olefin.[2] Although several transition metal-promoted processes based on early[2b,3] and late[4] transition metals are known, it seemed that an acid-catalyzed route could be developed.

Related methods for C−O bond formation using acid catalysis have been studied in great detail. Alkenes undergo hydration in moderately concentrated aqueous sulfuric acid to generate saturated alcohols.[5] However, the focus for the addition of electronically similar tosylamides has been on Hg(II)-mediated cyclizations of *N*-tosyl-4-pentenamines and use of β-silicon effect for acid-catalyzed cyclizations of sulfonamides tethered to allylsilanes.[6] During studies on

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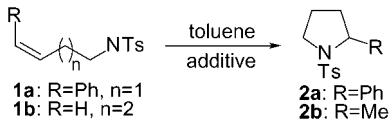
palladium-catalyzed hydroamination[7] of tosylamides, we discovered from control experiments a Brønsted acid-catalyzed cyclization that generates five- and six-membered heterocycles in good yield.

Our initial experiments showed that tosylamide **1a** cyclized in the presence of catalytic $Pd(PPh_3)_4$ and triflic acid. However, this reaction, in contrast to reactions of free amines, occurred in the absence of palladium to give **2a** in good yield (Table 1). In the absence of acid, no product was observed,

Table 1. Catalytic Cyclizations of **1a** and **1b**



1a: R=Ph, n=1
1b: R=H, n=2

2a: R=Ph
2b: R=Me

substrate	additive	time, h	temp, °C	yield, %[a]
1a	$Pd(PPh_3)_4$ (5%), TfOH (20%)	2	100	92
1a	TfOH (20%)	2	100	98
1a	none	24	100	0[b]
1a	TfOH (20%)	72	rt	65
1b	$Pd(PPh_3)_4$ (5%), TfOH (20%)	2	100	96
1b	TfOH (20%)	2	100	98
1b	none	24	100	0[b]
1b	TfOH (20%)	48	rt	75
1b	TFA (20%)	24	100	0[b]
1b	HOAc (20%)	24	100	0[b]
1b	C_6F_5COOH (20%)	24	100	0[b]
1b	Tf_2O (20%)	2	100	100
1b	H_2SO_4 (20%)	4	100	90

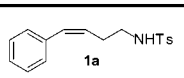
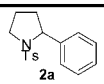
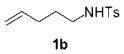
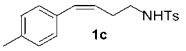
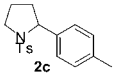
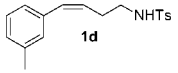
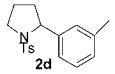
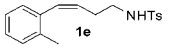
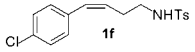
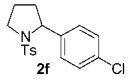
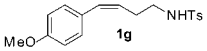
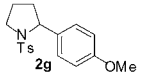
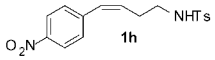
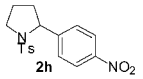
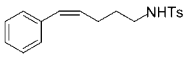
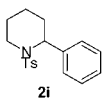
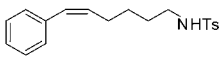
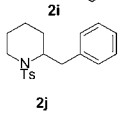
[a] Yield determined by ^1H NMR spectroscopy. 1,3,5-Trimethoxybenzene was used as internal standard. [b] Starting material was not consumed.

even upon prolonged heating at 100 °C in toluene. The acid-catalyzed cyclizations even proceeded at room temperature, although longer reaction times were required and lower yields were observed.

To test whether the benzylic cation that would be formed from protonation of **1a** at the olefin was required for cyclization, we evaluated acid-catalyzed reactions of the aliphatic substrate **1b**. Substrate **1b** also underwent the acid-catalyzed cyclization to form the Markovnikov cyclization product **2b**. After screening different acids, as summarized in Table 1, we concluded that those with a $pK_a \leq 10$ were sufficiently acidic to act as catalysts. In addition to triflic anhydride, sulfuric acid catalyzed this transformation. Reactions conducted in the presence of sulfuric acid as catalyst required slightly longer reaction times than did reactions in the presence of triflic acid.

A variety of substrates with different substitution patterns were prepared to evaluate the scope of the acid-catalyzed cyclizations. The precursors **1a** and **1c**−**j** were prepared from the corresponding aromatic aldehydes by a Wittig olefination.[8] Reactions of substrates **1a**−**j** are summarized in Table 2. Products **2a**−**f**, containing five-membered rings, were

Table 2. Acid Catalyzed Cyclizations of **1**

tosylamide	product	Method:[a] yield[b]
 **1a**	 **2a**	**A**: 83% (2h) **B**: 80% (4h)
 **1b**	 **2b**	**A**: 95% (2h) **B**: 77% (4h)
 **1c**	 **2c**	**A**: 77% (2h) **B**: 75% (4h)
 **1d**	 **2d**	**A**: 99% (2h) **B**: 90% (6h)
 **1e**	 **2e**	**A**: 81% (2h) **B**: 80% (10h)
 **1f**	 **2f**	**A**: 88% (2h) **B**: 93% (4h)
 **1g**	 **2g**	**A**: 0% (2h)[c] **B**: 27% (4h)
 **1h**	 **2h**	**A**: 0% (24h)[d] **B**: 0% (24h)[d]
 **1i**	 **2i**	**A**: 83% (2h) **B**: 80% (24h)
 **1j**	 **2j**	**A**: 51% (4h) **B**: 0% (24h)

[a] Method **A**: TfOH (20 mol %), 100 °C. Method **B**: H_2SO_4 (20 mol %), 100 °C. [b] Isolated yield after column chromatography. [c] Starting material decomposed completely. [d] Starting material was not consumed.

obtained in good yields, even though most of these transformations are unfavorable 5-*endo*-trig cyclizations, according to Baldwin's rules.[9] In addition, the six-membered ring **2i** was formed by a 6-*endo*-trig cyclization in excellent yield. Prolonged heating was necessary for reaction of **1i** in the presence of sulfuric acid as the catalyst. Substrate **1j**, which could form a seven-membered ring through an intermediate with benzylic stabilization or a six-membered ring through an unstabilized intermediate, formed the six-membered ring by a 6-*exo*-trig process. Although yields were low from reactions with either acid, reactions of the sensitive substrate **1g** gave higher yields when catalyzed by sulfuric acid than when catalyzed by triflic acid. The very electron deficient alkene **1h** did not react, presumably because the low Lewis basicity

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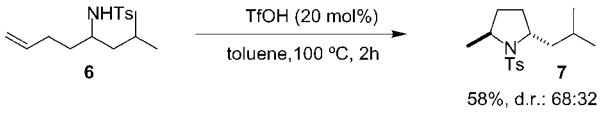
of the double bond makes it less susceptible to protonation. Reactions that would form three- or four-membered rings did not occur because of rapid decomposition of the allylic amine precursors under the strongly acidic conditions.[10]

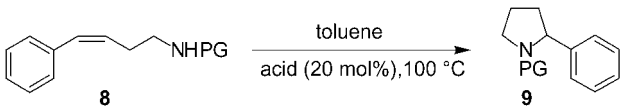
To investigate the diastereoselectivity of this new reaction, tosylamidoalkene **6** was prepared from the corresponding primary amine **5**. This amine was generated from the related alcohol **4** by a Mitsunobu reaction with phthalamide and deprotection.[11] Reaction of **6** in the presence of 20% triflic acid gave the 2,5-disubstituted pyrrolidine **7** with moderate diastereoselectivity. This diastereoselectivity favored the thermodynamically more stable *trans*-isomer (Scheme 1).

Scheme 1. Cyclization of **6**



Although several improved procedures for the deprotection of tosylamides have been reported,[12] other sulfonamides or amides are deprotected more easily. Thus, we sought acid-catalyzed cyclizations of aminoalkenes containing more labile activating groups. After screening nosylate **8a**, carbamates **8b** and **8c**, and amide **8d**, as well as free amine **8e**, we found that substrates containing the *p*-nitrophenylsulfonyl group gave the cyclization products in good yields (Table 3). Removal of this group has been accomplished under mild conditions.[13]

Table 3. Variation of Protecting Groups



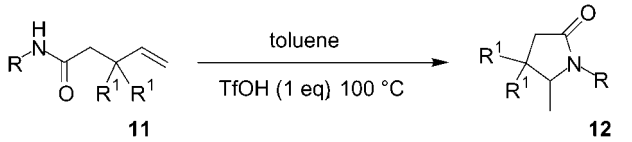
substrate	PG	acid	time, h	convn, %[a]	yield, %
8a	Ns	TfOH	4	100	95[b]
8a	Ns	H_2SO_4	100	84	58[b]
8b	Fmoc	TfOH	26	100	0
8b	Fmoc	H_2SO_4	26	37	0
8c	Cbz	TfOH	24	0	0
8c	Cbz	H_2SO_4	24	49	0
8d	Ac	TfOH	24	0	0
8d	Ac	H_2SO_4	24	32	0
8e	H	TfOH	26	0	0
8e	H	H_2SO_4	24	41	0

[a] Determined by NMR. 1,3,5-Trimethoxybenzene was used as internal standard. [b] Isolated yield after column chromatography.

We propose that the higher Lewis basicity of the amide or amine in substrates **8b**−**e** vs the sulfonamide in **1** and **6** prevents the reaction. The protonated carbonyl or amine is apparently not acidic enough to transfer its proton to the olefin. In addition, an analogue of substrate **8a**, but containing a *m*-pyridyl (**10**) instead of phenyl group, did not undergo cyclization. Moreover, addition of pyridine or pyridine *N*-oxide to reactions of **1a** completely suppressed cyclization.

To evaluate the potential of the process to form lactams and to elucidate further the influence of the electronic properties of the nitrogen and activating group on this reaction, we prepared benzamides **11a**−**e** in Table 4. The

Table 4. Cyclization of Amides



substrate	R	R^1	time, h	yield, %[a]
11a	Ph	H	30	99
11b	*p*-tolyl	H	30	99
11c	Ph	Me	5	99
11d	*p*-tolyl	Me	5	99
11e	*p*-nitrophenyl	H	1	0[b]

[a] Isolated yield. [b] *p*-Nitroaniline was isolated.

electron-deficient benzamides should not be as prone to protonation as the *N*-alkyl amide **8d** in Table 3. Indeed, γ-lactams **12a**−**d** were obtained in essentially quantitative yields when the reactions were conducted in the presence of stoichiometric amounts of triflic acid. We presume that stoichiometric amounts of acid were required because the protonated *N*-alkyl amide product is too weakly acidic to initiate cyclization of a second starting benzamide. Reactions were faster with the branched substrates **11c** and **11d**. Nitrophenyl substrate **11e** underwent cleavage of the amide bond to form *p*-nitroaniline (Table 4). Nicolaou has reported similar transformations using IBX as reagent. The IBX- and acid-promoted reactions probably proceed by different pathways.[14]

Several observations argue against a simple mechanism involving direct protonation of the olefin by triflic acid and

(10) **Representative procedure:** Compound **1a** (301 mg, 1.00 mmol) was dissolved in 1.0 mL of toluene in a screw-cap vial equipped with a stir bar. Trifluoromethanesulfonic acid (17.6 μL, 30.0 mg, 0.263 mmol) was added by syringe, and the vial was placed in an oil bath at 100 °C. After 2 h, the mixture was allowed to cool to room temperature. Triethylamine (0.5 mL) was added, and the crude mixture was subjected to flash chromatography on neutral alumina (hexanes/ethyl acetate 40/60). Compound **2a** (250 mg, 83%) was obtained as a colorless solid. ^{1}H NMR: δ = 1.60−1.70 (m, 1H), 1.72−1.85 (m, 2H), 1.90−2.00 (m, 1 H), 2.40 (s, 3H), 3.35−3.45 (m, 1H), 3.55−3.65 (m, 1H), 4.78 (dd, J = 3.5, 8.0 Hz, 1H), 7.15−7.35 (m, 7H), 7.60−7.70 (m, 2H). ^{13}C NMR: δ = 21.5, 23.9, 35.8, 49.4, 63.3, 126.1, 127.0, 127.5, 128.3, 129.6, 135.1, 143.0, 143.2, 161.5.

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intramolecular trapping of the carbenium ion with the pendant tosylamide. If protonation of the olefin by triflic acid were rate-limiting, then substrates that form five- and six-membered rings would react at a similar rate. In contrast, **1a** and **1i** required 4 and 24 h to form pyrrolidine and piperidine products when sulfuric acid was the catalyst.

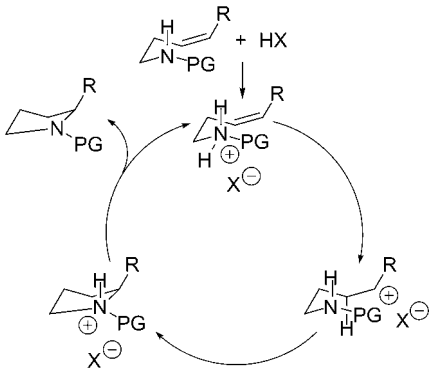
Reversible protonation and rate-limiting, intramolecular attack of the sulfonamide would be consistent with these different rates. However, our data also argue against reversible protonation of the olefin. First, no isomerization of the *Z*-olefin in the nosylamido substrate **8a** was observed when its cyclization was monitored carefully by ^{1}H NMR spectroscopy. Moreover, addition of triflic acid to *cis*-stilbene in toluene, the solvent of the cyclization reactions, led to formation of the Markovnikov, Friedel−Crafts addition product without isomerization of unreacted olefin to *trans*-stilbene. β-Methylstyrene formed the analogous product from addition to toluene when treated with triflic acid, and this reaction was faster than cyclization of alkenyl sulfonamides.

Therefore we investigated whether triflic acid is consumed by protonation of the sulfonamide. If so, then the protonated sulfonamide and not the free triflic acid would initiate cyclization by an intramolecular proton transfer. The reaction rate would then depend on ring size, and the intramolecular trapping of the carbocation with the sulfonamide could be faster than trapping with arene solvent.

To test the basicity of the tosylamide in this medium, we added triflic acid to *N*-methyl-*p*-toluenesulfonamide in benzene-d_6. The degree of protonation was determined by monitoring the ^{1}H NMR chemical shift of the *N*-methyl group as triflic acid was added. The plot of chemical shift vs equiv of acid (see Supporting Information) showed a linear increase in chemical shift until 1 equiv of triflic acid is added, at which point the chemical shift decreased. These data suggest that a full equivalent of triflic acid is consumed by protonation of *N*-methylsulfonamide.[15]

Therefore, we propose that the cyclization (Scheme 2) begins with an alkenyl tosylamide that is protonated at either the nitrogen or oxygen of the tosylamide group. The proton would then be transferred intramolecularly to the double bond in the rate-determining step. Trapping of the cation by the sulfonamide and transfer of the proton from the product to the sulfonamide of another reactant would complete the catalytic cycle.

Scheme 2. Proposed Catalytic Cycle



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Supporting Information Available: General experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A reviewer expressed concern that the strong acid could react directly with the arene. The leveling effect from protonation of the sulfonamide would discourage this process, and the low concentration of acid and absence of SO_3 in reactions catalyzed by sulfuric acid prevent arene sulfonation.