JOC Article

Intramolecular Additions of Various π-Nucleophiles to Chemoselectively Activated Amides and Application to the Synthesis of ( )-Tashiromine

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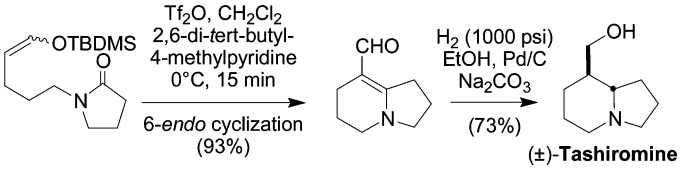

Vilsmeier Haack type cyclizations proved to be particularly efficient for generating parts of the polycyclic cores of many alkaloids, although only monocyclizations have so far been reported. With the goal of rapidly and efficiently constructing polycyclic alkaloids, we decided to exploit the Vilsmeier Haack reaction by utilizing iminium ions successively generated and trapped with tethered nucleophiles. To develop such a strategy, we had to set the first cyclization. This constitutes a great challenge in itself because amide activation conditions are usually not compatible with tethered nucleophiles, except for indoles and aromatic rings which have already been reported. This paper describes the comprehensive study of intramolecular addition of silyl enol ethers, allylsilanes, and enamines to chemoselectively activated formamides, aliphatic amides, and lactams. Good to excellent yields were obtained for the 5-*exo,* 6-*exo*, and 6-*endo* modes of cyclization. Moreover, we demonstrated that the species in solution after the cyclization are iminium ions. This is highly encouraging for the development of bis-cyclization strategies. An expeditious total synthesis of ( )-tashiromine is also reported.

Introduction

Alkaloid natural products have very diverse structures, many of which are polycyclic, and show an extremely wide span of interesting biological activities. This renders alkaloids very attractive to synthetic chemists and has been a great source of motivation for the finding of synthetic strategies and reactions to construct such complex molecules. In that sense, iminium ions are certainly among the functional groups most widely used in total syntheses of alkaloids, especially the intramolecular Mannich reaction, or Mannich cyclization, which proved to be extremely efficient at putting together the heterocyclic skeleton of numerous alkaloids.[1] Numerous methods of generating iminium ions for the Mannich reaction have been developed over the years,[2] and these iminium ions are of oxidation state II (two C-heteroatom bonds) by definition. The use of iminium ions of a higher oxidation state are known as the Vilsmeier Haack reaction. These iminium ions are usually derived from amides, by various activation means employing oxophilic reagents.[3,4]

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(1) (a) *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1976, part I; 1979, part 2. (b) Overman, L. E.; Ricca, D. J. In *Comprehensi e Organic Synthesis*; Trost, B. M., Flemming, I., Heathcock, C. H., Eds; Pergamon: Oxford, UK, 1991; Vol. 2, p 1007.

(2) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Re .* **2004**, *104*, 2311.

(3) For various amide activation conditions, see: (a) Nishiyama, H.; Nagase, H.; Ohno, K. *Tetrahedron Lett.* **1979**, *48*, 4671. (b) Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875. See also references cited in: (c) Kuhnert, N.; Clemens, I.; Walsh, R. *Org. Biomol. Chem.* **2005**, *3*, 1694. (d) Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348.

(4) For addition of heteroatomic nucleophiles to activated amides, see: (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163. (b) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499. (c) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. (d) Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677. (e) Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R. *Tetrahedron Lett.* **1998**, *39*, 711. (f) Thomas, E. W. *Synthesis* **1993**, 767.

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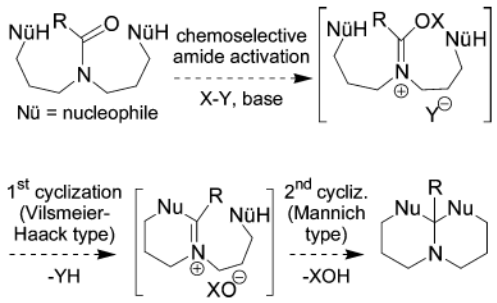
SCHEME 1. Planned Biscyclization Strategy



A screening of the literature revealed that iminium ions of both oxidation states are only used in monocyclizations, which is a limit inherent in the oxidation state of the iminium ion only in the Mannich cyclization. However, the higher oxidation state of the iminium ion in the Vilsmeier−Haack type cyclization incited us to exploit the idea of performing two sequential cyclizations in a single operation utilizing iminium ions successively generated and trapped with tethered nucleophiles (NüH, Scheme 1). This strategy offers the possibility of generating polycyclic alkaloid skeletons in one step from simple amide substrates. A very limited number of sequential iminium ion cyclizations have been reported, but these cyclizations were not performed on the same iminium carbon.[5] Our strategy would thus additionally allow for the creation of a tertiary or a quaternary center α to nitrogen in the final product from an initial secondary of tertiary amide, respectively. Because the cyclization substrates are made from amides or lactams, connections of diverse branches containing the nucleophiles should be facile using well-known chemistry. Modulations of the branches and their position could furthermore lead to a vast assortment of polycyclic alkaloid skeletons, rendering such a strategy highly attractive for its straightforwardness and potential application in total synthesis.

A major challenge to the development of our strategy is, however, to find chemoselective amide activation conditions compatible with the required tethered nucleophiles. The amide activation conditions generally use, or generate during the reaction, Lewis or Bronsted acids[3] that would easily destroy or deactivate nucleophiles such as vinylsilanes, allylsilanes, enol ethers, enamines, amines, thiols, alcohols, etc. This is probably why only indoles[6] or activated benzene rings[7] have been so far reported to intramolecularly trap activated amides, whereas all other reported nucleophiles are externally added once the amide activation is completed.[4,3d]

We recently published our preliminary successful results for amide activation and cyclization with tethered carbon nucleophiles other than indoles or benzene rings.[8] We now wish to report the full account of this work emphasizing general trends that emerged from detailed comparisons between the different nucleophiles we used, the nature of the amide substrates, and ring sizes generated.

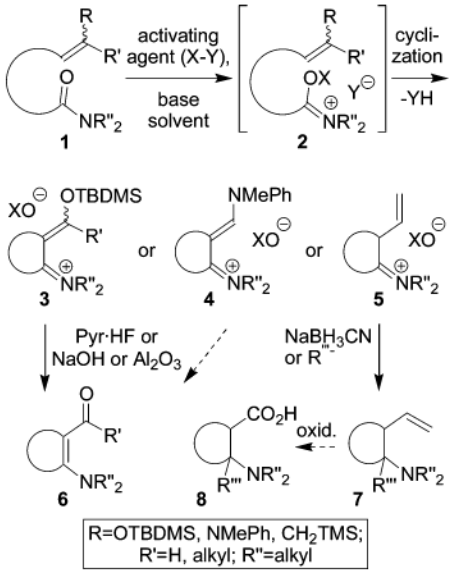
(5) For selected examples, see: (a) Jackson, A. H.; Shannon, P. V. R.; Wilkins, D. J. *Tetrahedron Lett.* **1987**, *28*, 4901. (b) He, F.; Bo, Y.; Altom, D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.

(6) Typically the Bischler−Napieralski cyclization: Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 903.

(7) (a) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659. (b) Martinez, A. G.; Alvarez, R. M.; Barcina, J. O.; Cerero, S. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571.

(8) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *Org. Lett.* **2005**, *7*, 4431.

SCHEME 2. Representative Chemoselective Amide Activation and Nucleophilic Cyclization



The key reaction is presented in Scheme 2 with a representative amide substrate **1** tethered to a π-nucleophile. When the nucleophile is an aldehydic silyl enol ether (**1**, R = OTBDMS, R′ = H) or a ketonic silyl enol ether (**1**, R = OTBDMS, R′ = alkyl), a cyclic enaminal or enaminone[9] **6** is formed, respectively. Enamines (**1**, R = NMePh) lead to vinylogous amidinium ions **4**, that could for instance be hydrolyzed to the corresponding enaminals **6**, whereas allylsilanes (**1**, R = CH_2TMS) lead to amines **7** α to a tertiary ($NaBH(OAc)_3$ quench, R‴ = H) or potentially quaternary center (C-nucleophile addition, R‴ = alkyl), which could both be derived to the corresponding chiral β-amino acids **8**.

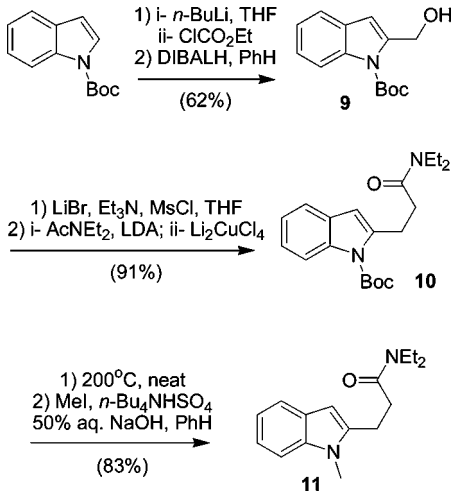
Results and Discussion

The following sections will first describe the syntheses of all of the cyclization substrates, followed by the optimization of the amide activation−cyclization conditions on a particular substrate and the application of these conditions to the intramolecular 5-*exo*, 6-*exo*, 5-*endo*, and 6-*endo* additions of tethered silyl enol ethers, allylsilanes, and enamines to chemoselectively activated amides and lactams. An application of our new strategy to the synthesis of tashiromine will finally be presented.

Synthesis of Indole Substrate 11. To compare the various nucleophiles we elected to study with the indole ring used in the typical Bischler−Napieralski cyclization, we synthesized the 5-*exo* cyclization substrate **11** (Scheme 3). Starting from Boc-protected indole, an ortho lithiation and quench with methyl chloroformate gave the indole ester, which was then reduced to the alcohol **9** in 59% overall yield. Bromination and displacement with the copper enolate of *N*,*N*-diethylacetamide furnished the amide **10**.[10] We then pyrolyzed the Boc and methylated the nitrogen to furnish the desired product **11** in 83% yield.[11] Although **11** was successfully activated and cyclized (vide infra), an attempted amide activation of **10** and

(9) Enaminones are particularly interesting and versatile intermediates used for natural product synthesis. See: Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979.

SCHEME 3. Synthesis of the Indole Substrate



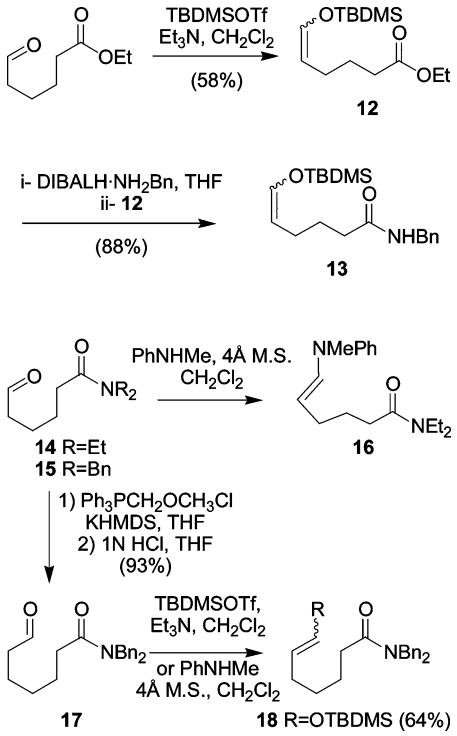
indole trapping of the resulting iminium ion was not productive, presumably because of the poor nucleophilicity of the Boc-protected indole.

Synthesis of 5- and 6-*exo* Cyclization Substrates.[12] The chosen 5- and 6-*exo* cyclization substrates contain either an amide or a lactam as the iminium ion precursor, giving rise to either monocyclic or bicyclic adducts. The synthesis of the secondary amide compound **13** started with the formation of the silyl enol ether **12** from the known ethyl 6-oxohexanoate,[13] using TBDMSOTf (Scheme 4). A DIBALH benzylamine complex[14] was then used to convert the ester **12** to the required secondary amide **13**. A series of tertiary amides was also prepared. The enamine **16**[15] was formed by the condensation of *N*-methylaniline with the known aldehyde **14**,[16] whereas the silyl enol ether **18** was derived from the aldehyde **17** generated by a Wittig olefination of **15**[8] and hydrolysis of the resulting methyl enol ether in 93% yield for these two steps.

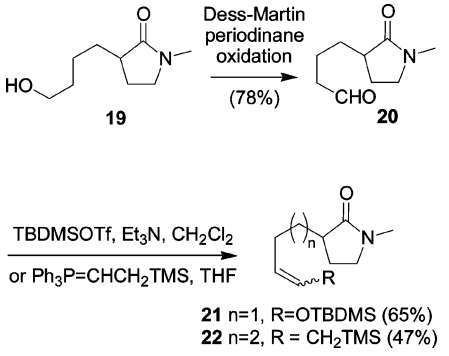
A series of lactams was also prepared, starting with the oxidation of the C-branched *N*-methylpyrrolidinone **19** (Scheme 5). The resulting aldehyde **20** was then subjected to TBDMSOTf to give the corresponding silyl enol ether **21**, or olefinated[17] to the allylsilane **22** in good yields.

Synthesis of 5- and 6-*endo* Cyclization Substrates.[12] The preparation of the 5- and 6-*endo* cyclization substrates containing an amide started with a condensation reduction sequence

SCHEME 4. 5- and 6-*exo* Cyclization Amide Substrates



SCHEME 5. 5- and 6-*exo* Cyclization Lactam Substrates



performed on the aldehyde **23**[18] to generate the secondary amine **26** (Scheme 6). The four carbon analogue **25** was obtained by the *N*-alkylation of benzylamine with the iodide **24**.[19] A sequence of *N*-acetylation, acidic methanolysis of the silyl ethers **27** and **28**, and Swern oxidation furnished the desired aldehydes **29** and **30** respectively in high yields. They were both transformed to the corresponding silyl enol ethers **31** and **32** by using either TBDMSOTf with a weak base (Et_3N) or TBDMSCl with a stronger base (KHMDS). Each of these silylation conditions were empirically determined to be the most suitable for these aldehydes.

Finally, we prepared lactams branched on nitrogen with an allylsilane or an enamine as the tethered nucleophiles. The known aldehyde **34**[8] was condensed with *N*-methylaniline to give the desired enamine **35**, whereas the aldehyde **33**[8] was subjected to the Seyferth Wittig olefination to furnish the allylsilane **36** as a 3:1 ratio of geometric isomers (Scheme 7).

(10) The lithium enolate, from LDA deprotonation of *N*,*N*-diethylacetamide, gave less than 20% yield of alkylated product **10**. Addition of lithium chlorocuprate was essential for the success of this reaction. For use of Li_2CuCl_4 as catalyst for enolate alkylations, see: Gelin, J.; Mortier, J.; Moyroud, J.; Chene, A. *J. Org. Chem*. **1993**, *58*, 3473.

(11) We also tried the same sequence of reactions but starting with *N*-methylindole instead of *N*-Boc-indole. It turns out that the bromo derivative was too unstable and could not be purified before the nucleophilic displacement with the acetamide copper enolate.

(12) The use of *exo* and *endo* in this paper refers to the amide portion of the substratres. For a more appropriate description of cationic cyclizations involving -nucleophiles, see: (a) Ben-Ishai, D. *J. Chem. Soc.*, *Chem. Commun.* **1980**, 687. (b) Lochead, A. W.; Proctor, G. R.; Caton, M. P. *J. Chem. Soc.*, *Perkin Trans. 1* **1984**, 2477.

(13) Taber, D. F.; Teng, D. *J. Org. Chem.* **2002**, *67*, 1607.

(14) Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039.

(15) This enamine was unstable, as aldehydic enamines usually are, and had to be used without further purification in the cyclization step. Only the trans enamine was formed.

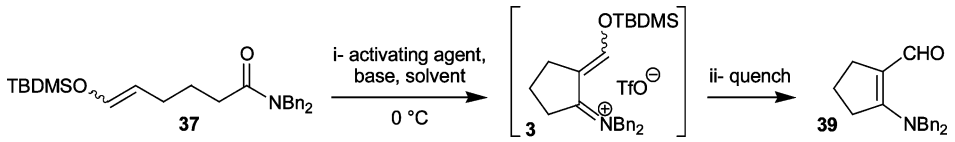
(16) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066.

(17) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446.

(18) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.

(19) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467.

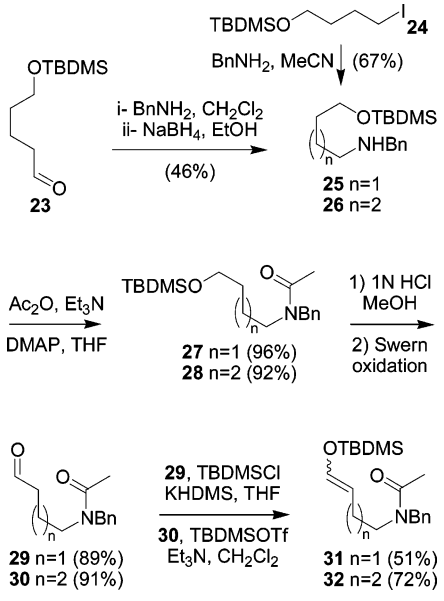
TABLE 1. Optimization of the Chemoselective Amide Activation and 5-*exo* Cyclization with Substrate 37



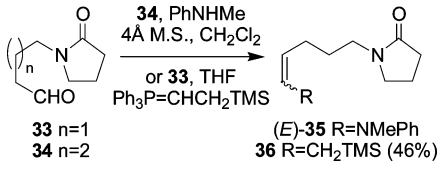
entry	activating agent (1.1 equiv)	base (1.1 equiv)	solvent (0.1 M)	quench	yield of **39**
1	$POCl_3$	$^iPr_2NEt$	CH_2Cl_2	NaOH	0% (**15** was the only identifiable product)
2	$(CF_3CO)_2O$	DTBMP[a]	CH_2Cl_2	NaOH	0% (decomposition)
3	$(CCl_3O)_2CO$	$^iPr_2NEt$	CH_2Cl_2	NaOH	0% (**15** was the only identifiable product)
4	TMSOTf	$^iPr_2NEt$	CH_2Cl_2	NaOH	0% (55% of **38**)
5	BrCOCOBr	DTBMP[a]	CH_2Cl_2	NaOH	0% (3% of **15** 7% of **38**)
6[b]	**Tf_2O**	**DTBMP**[a]	**CH_2Cl_2**	**NaOH**	**89%**
7	Tf_2O[c]	pyridine[d]	CH_2Cl_2	NaOH	0% (no reaction)
8	Tf_2O	pyridine	CH_2Cl_2	NaOH	46%
9	Tf_2O	DMAP[e]	CH_2Cl_2	NaOH	16% (32% of **38**)
10	Tf_2O	$^iPr_2NEt$	CH_2Cl_2	NaOH	85%
11	Tf_2O	none	CH_2Cl_2	NaOH	31% (28% of **38**)
12	Tf_2O	DTBMP[a]	toluene	NaOH	63% (11% of **38**)
13	Tf_2O	DTBMP[a]	1,4-dioxane	NaOH	28% (26% of **38**)
14	Tf_2O	DTBMP[a]	CH_2Cl_2	Pyr HF	85%
15	Tf_2O	DTBMP[a]	CH_2Cl_2	MeONa	65%
16	Tf_2O	$^iPr_2NEt$	CH_2Cl_2	$^nBu_4N$ F	57%
17	Tf_2O	$^iPr_2NEt$	CH_2Cl_2	Al_2O_3	55%

[a] DTBMP: 2,6-di-*tert*-butyl-4-methylpyridine. [b] Taken from ref 8. [c] 1.3 equiv, 50 to 0 °C. [d] 1.3 equiv. [e] DMAP: 4-(*N*,*N*-dimethylamino)pyridine.

SCHEME 6. 5- and 6-*endo* Cyclization Amide Substrates



SCHEME 7. 6-*endo* Cyclization Lactam Substrates



Optimization of the Chemoselective Amide Activation and Cyclization. Four different parameters were studied to set up the most convenient and reproducible reaction conditions for amide activation without altering the tethered nucleophile: (1) the nature of the activating agent,[20] (2) the need for and the nature of the base, (3) the solvent, and (4) the neutralization (quench)[20] of the resulting iminium ions (cf. **3**, scheme in Table 1). A study of all of these variables was conducted on the previously reported 5-*exo* cyclization substrate **37**[8] and the results are presented in Table 1.

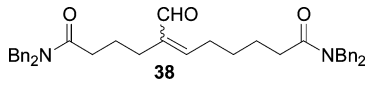


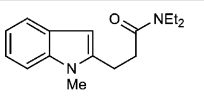
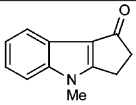
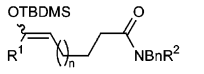
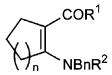
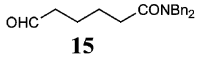
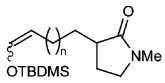
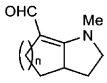
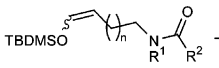
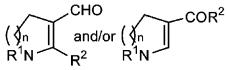
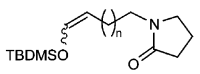
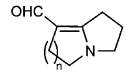
FIGURE 1. Aldol product **38** from activation of substrate **37**.

Many activating agents are known to generate iminium ions from amides.[3] However, most of them proved to be incompatible with the acid sensitive silyl enol ether present on compound **37**. For example, $POCl_3$ (entry 1), TFAA (entry 2), and triphosgene (entry 3) all destroyed the silyl enol ether prior to amide activation, leading to the corresponding aldehyde **15** or to decomposition. With TMSOTf (entry 4), the silyl enol ether moiety was partially cleaved during the reaction and the aldol product **38** was obtained in 55% yield and was fully characterized (Figure 1). The same byproducts (aldehyde **15** and aldol product **38**) were obtained in the case of activation with oxalyl bromide, albeit in much lower yields (3% and 7%, respectively, entry 5). The best activating agent proved to be Tf_2O (entry 6). The intermediate iminium ion **3** (cf. scheme in Table 1) was characterized by ^1H NMR spectroscopy and gave, after a sodium hydroxide hydrolysis, the desired enaminal **39** in 89% yield (entry 6).

The effect of the base was also surveyed. Excess of pyridine (3 equiv) at low temperature (50 to 0 °C, Table 2, entry 7)[4c] gave no reaction at all. The same base (1.1 equiv) used at 0 °C furnished a 46% yield of the desired adduct (entry 8). This modest yield could arise from a partial reaction of pyridine with Tf_2O at that temperature, resulting in the formation of *N*-triflylpyridinium triflate, which is a weaker activating agent than

(20) For this screening, the base used was either 2,6-di-*tert*-butyl-4-methylpyridine or diisopropylethylamine. This is not critical, since entries 6 and 10 of Table 1 gave essentially the same cyclization yield for both of these bases.

TABLE 2. Cyclization of Indole and Silyl Enol Ethers on Activated Amides and Lactams

entry	substrate	product	cycliz. type	activation condition[a]	yield using 1 N NaOH quench[b]	yield using Pyr·HF quench[c]
1			5-*exo*	A	89%	---
2	**11**	**45**	5-*exo*	B	78%	---
						
3	**13** R^1=H, R^2=H, n=1	**46**	5-*exo*	C	37%	29%
4[d]	**37** R^1=H, R^2=Bn, n=1	**39**	5-*exo*	D	89%	85%
5[d]	**40** R^1=Ph, R^2=Bn, n=1	**47**	5-*exo*	D	80%	43%
6	**18** R^1=H, R^2=Bn, n=2	**48**	6-*exo*	D	35%	51%
7	**18** R^1=H, R^2=Bn, n=2	**48**	6-*exo*	D	55%, Al_2O_3 quench[e]	
8	 **15**	**39**	5-*exo*	E	24%	---
						
9	**21** n=1	**49**	5-*exo*	D	29%	57%
10[d]	**41** n=2	**50**	6-*exo*	D	32%	81%
						
11	**31** R^1=Bn, R^2=Me, n=1	**51** **52**	5-*endo*	D	13% of **51** +23% of **52**	39% of **51**
12	**32** R^1=Bn, R^2=Me, n=2	**53**	6-*endo*	D	34%	71%
13[d]	**42** R^1=Me, R^2=H, n=2	**54**	6-*endo*	D	78%	63%
						
14[d]	**43** n=1	**55**	5-*endo*	D	35%	29%
15[d]	**44** n=2	**56**	6-*endo*	D	93%	73%

[a] Reagents and conditions: (A) Tf_2O, DMAP, CH_2Cl_2, reflux; (B) $POCl_3$, $ClCH_2CH_2Cl$, reflux; (C) Tf_2O, Pyr, CH_2Cl_2, 50 to 0°C, 3 h; (D) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0°C, 15 min; (E) TMSOTf, $^iPr_2NEt$; Tf_2O. [b] 1 N NaOH, THF, 25°C, 15 h. [c] Pyr HF, 0 °C, 1 h. [d] Taken from ref 8. [e] Basic Al_2O_3, rt, 1 h.

Tf_2O toward amides.[4c] The same reaction of Tf_2O with the base was observed when 4-(*N,N*-dimethylamino)pyridine was used and the even less reactive *N*-triflyl-4-(*N,N*-dimethylamino)pyridinium triflate could account for the poor 16% yield of entry 9.[21] That side reaction was, however, not encountered when Hünig's base (entry 10) or 2,6-di-*tert*-butyl-4-methylpyridine (entry 6) were used. The latter gave the cleanest conversion and only 1.1 equiv of base was necessary. The reaction was also run in the absence of base (entry 11) and still gave the desired cyclized product **39** without extensive cleavage of the nucleophilic moiety by the triflic acid produced,[22] but the yield was lower (31%) and the conversion was less clean.

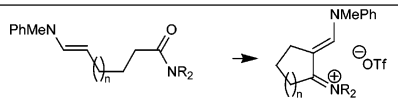
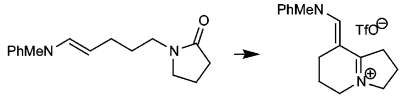
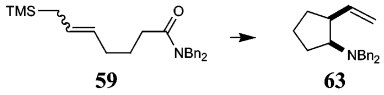
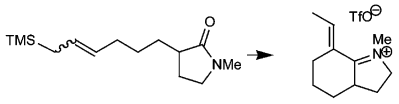
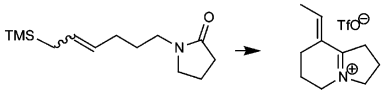
The solvent also has a significant effect on the yield of the reaction. Dichloromethane was by far the best solvent, giving rise to 89% of the desired enaminal **39** without any formation of the aldol byproduct **38** (entry 6). Interestingly, the nonpolar solvent toluene still gave a good yield (63%) of cyclized product **39**, accompanied by 11% of aldol product **38** (entry 12). The proportion of the aldol product was even higher when 1,4-dioxane was used, giving an almost 1:1 ratio of enaminal **39** and aldol product **38** (54% combined yield, entry 13).

Finally, to our surprise, the most crucial parameter to control to get high yields of the desired cyclized product **39** turned out to be the cleavage of the silyl group on the iminium ion intermediate **3** in the quench procedure (cf. scheme in Table 1).[20] Pyr HF and NaOH gave very similar results for this substrate (Table 1, 85% and 89%, entries 14 and 6, respectively), although this was not found to be true for all the cyclized products as will be shown (Tables 2 and 3). With sodium methoxide, a moderate 65% yield was observed (Table 1, entry 15). An additional drop in the yield occurred when tetrabutyl-

(21) A white precipitate is formed in the reaction vessel as soon as Tf_2O is added to the solution of **37** and 4-(*N,N*-dimethylamino)pyridine.

(22) As observed on ^1H NMR spectra of aliquots of the reaction.

TABLE 3. Cyclization of Enamines and Allylsilanes on Activated Amides and Lactams

entry	substrate	product	cyclization type	activation condition[a]	yield, quench
1[b]	 **58** R=Bn, n=1	**60**	5-*exo*	A	74% (from **15**)[c]
2	**16** R=Et, n=1	**61**	5-*exo*	A	78% (from **14**)[c]
3	 **35**	**62**	6-*endo*	A	78% (from **34**)[c]
4[b]	 **59**	**63**	5-*exo*	B	81% (94 : 6 *syn* : *anti*), $NaBH(OAc)_3$[d]
5	 **22**	**64**	6-*endo*	B[e]	93%[f,c]
6	 **36**	**65**	6-*endo*	B[e]	70%[f,c]

[a] Reagents and conditions: (A) Tf_2O, CH_2Cl_2, 0°C, 20 min; (B) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0°C, 15 min. [b] Taken from ref 8. [c] Concentrated then purified directly. [d] $NaBH_3CN$, 78 to 0 °C, 15 h. [e] 15 h. [f] $ClCH_2CH_2Cl$, reflux, 15 h.

ammonium fluoride (57% yield, entry 16) or basic alumina (55% yield, entry 17) was used. We do not fully understand the large influence of the quench reagents on the reaction yield, but a possible explanation could be the ease with which highly water soluble hydrates form in certain quench conditions, as will be discussed below.

5-*exo*, 6-*exo*, 5-*endo*, and 6-*endo* Cyclizations of Various Tethered Nucleophiles on Amides and Lactams. The optimized cyclization conditions were applied to the cyclization of other 5-*exo* cyclization substrates, as well as to 6-*exo*, 5-*endo*, and 6-*endo* cyclization substrates (Tables 2 and 3). In the case of substrates containing a silyl enol ether branch (Table 2), Pyr HF and NaOH were systematically used to cleave the silyl group on the iminium ion intermediate in the quench procedure (cf. **3**, scheme in Table 1), whereas other quench procedures specifically noted were used in the cases of substrates tethered to an enamine or an allylsilane (Table 3).

Comparison of the Cyclization Types (5- or 6-, *exo* or *endo*). A comparison could be made over four cyclization types only with silyl enol ether nucleophiles, tethered to aliphatic amides or to lactams (Table 2). For comparison purposes, we looked at the yields obtained with the Pyr HF quench. Only in the case of the activation of aliphatic amides and cyclization did the yields indicate that the 5-*exo* mode is by far the best (85%, entry 4), followed by the 6-*endo* (71%, entry 12), the 6-*exo* (51%, entry 6), and the 5-*endo* (39%, entry 11) modes. This order was somewhat different with lactams: the 6-*exo* mode is the best (81%, entry 10), followed by the 6-*endo* (73%, entry 15), the 5-*exo* (57%, entry 9), and the 5-*endo* (29%, entry 14) modes.

However, the yields obtained with the NaOH cleavage of the silyl group on the iminium ion intermediate in the quench procedure (cf. **3**, scheme in Table 1) show significant variations. The most remarkable example is with the 6-*exo* cyclization substrate **41** (entry 10, Table 2). Although the cyclization was always complete and very clean, as indicated by the analysis of ^1H NMR spectra of reaction aliquots, the hydrolysis step was particularly problematic. In fact, the bicyclic enaminal **50** was obtained in a much lower yield with a NaOH quench (32%) than with a Pyr HF quench (81%). Intrigued by that result, we stirred pure 6-*exo* cyclization product **50** in a 1:1 mixture of THF and water for 15 h and observed a complete loss of the product (the yield dropped to 0%). Evaporation of the aqueous phase led to various unidentifiable products. We suggest that a polar, water soluble carbonyl hydrate with strong hydrogen bonding might be responsible for the loss of material (Figure 2). The formation of a stable hydrate may also account for the difference in yields of the 6-*exo* cyclization of silyl enol ether substrate **18**. Again, the Pyr HF quench was superior to the NaOH quench (51% and 35% yield, respectively, entry 6, Table 2), although a basic alumina quench was even better (55% yield, entry 7). Such hydrogen bond stabilized hydrates are impossible for the *endo* cyclization products with allylsilanes or enamines (cf. Table 3, entries 6 and 3, respectively).

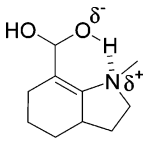
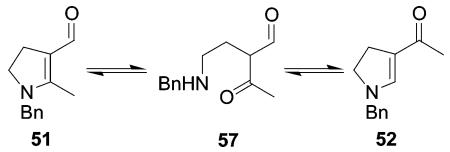


FIGURE 2. Proposed water soluble carbonyl hydrate of **50**.

Although this explains well the difference in yields of the two quench procedures applied to the same products for the

SCHEME 8. Proposed Mechanism for the Rearrangement of 51 to 52 in 1 N NaOH



cleavage of the silyl group on the iminium ion intermediate, it does not explain all of the differences observed. For example, while enaminal **51** was the only product formed when the Pyr HF quench was used, a rearranged product **52** appeared with the NaOH quench (entry 11, Table 2). In theory, the enaminal **51** should be the only product of a direct cyclization of the silyl enol ether moiety onto the activated amide of **31**. We suggest that compound **51** arises from the 1,4-addition of hydroxide anion to the enal of **52**, followed by the ring opening to the amino -keto aldehyde **57**, and condensation of the amine with the aldehyde (Scheme 8). This hypothesis was confirmed: mixtures of compounds **51** and **52** were observed when both **51** and **52** were treated independently with 1 N NaOH.

The hydrolysis problems were not encountered in the case of the enamines and the allylsilanes we cyclized (Table 3) and should allow for a more accurate comparison between the cyclization modes. However, the yields given for the enamines include their in situ preparation from the corresponding aldehydes, which are not uniform over the different substrates. Thus, we could not draw any precise conclusion about the ease of cyclization of enamines for the different modes of cyclization. In the case of the activation and cyclization of lactams tethered to allylsilanes, the 6-*exo* mode (93% yield, entry 5) proved to be more efficient than the 6-*endo* mode (70% yield, entry 6), following the trend observed with the silyl enol ethers (entries 10 and 15, Table 2, with the Pyr HF quench). Although the cyclizations of silyl enol ether onto aliphatic amides or lactams were all completed within 15 min, cyclizations of allylsilanes onto activated lactams were much slower (15 h) than on the activated amide (15 min). This is probably due to a higher steric congestion of lactams (additional substitution to lactam carbonyl) compared to the aliphatic amide and a lower reactivity of the allylsilane compared to the TBDMS enol ether, resulting in a higher sensitivity of the allylsilane to steric hindrance (earlier transition state with TBDMS enol ether than with allylsilane).

Comparison of the Nucleophiles. A series of tethered nucleophiles were screened with use of substrates that cyclized by the same mode (5/6-*endo*/*exo*) and having the same amide or lactam. All enolizable carbonyl groups (ketones and -keto-esters, not tabulated) we tested proved to be incompatible with the amide activation conditions: either the enol tautomer was more reactive than the amide toward the activating agent, or the activated amide could not be trapped with the enolized carbonyl.[23] We obtained the best results with silyl enol ethers, enamines, and allylsilanes, as shown in Tables 2 and 3. For the 5-*exo* cyclizations, the silyl enol ether **37** gave the highest yield (89%, entry 4, Table 2), followed by the allylsilane **59** (81%, entry 4, Table 3) and the enamine **58** (74%, entry 1, Table 3). This order was somewhat different with 6-*endo* cyclizations of lactams **44** (silyl enol ether, 93%, entry 15, Table 2), **35** (enamine, 78%, entry 3, Table 3), and **36** (allylsilane, 70%, entry 6, Table 3) or with 6-*exo* cyclizations of lactams **22** (allylsilane, 93%, entry 5, Table 3) and **41** (silyl enol ether, 81%, entry 10, Table 2). Intriguingly, this order does not reflect the -nucleophilicity tabulated by Mayr,[24] which places enamines on top of the list, followed by silyl enol ethers then allylsilanes. Because we could not report yields for the cyclization step only,[25] we cannot make a precise correlation between the -nucleophilicity of the tethered nucleophiles used and the yields of cyclized products.

As enamines were prepared from the corresponding aldehydes and cyclized one-pot, we wanted to see if the same could be done with silyl enol ethers. In entry 8 of Table 2, the aldehyde **15** was silylated with TMSOTf in the presence of a base, then Tf_2O was added to the reaction mixture without isolation of the silyl enol ether intermediate. After hydrolysis, the enaminal **39** was isolated in 24% yield (NaOH quench), compared to a 53% overall yield for the stepwise silylation (60% yield, ref 8) and cyclization (89% yield, entry 4, Table 2). There is thus an obvious advantage of preparing the silyl enol ether in a separate operation, before the cyclization. Looking at the result obtained from the one-pot preparation and cyclization of enamine **58** (entry 1, Table 3), it seems that the enamine formation is much more compatible with the following one-pot activation cyclization step than is the silyl enol ether formation.

After a Pyr HF quench, the ketonic silyl enol ether **40** cyclized in about half the yield of that obtained with the corresponding aldehydic silyl enol ether **37** (Table 2, entries 5 and 4, 43% and 85% yield, respectively), although this difference was less important when a NaOH quench was used (80% and 89% yield, respectively). These results indicate a small influence of the substitution of the silyl enol ether on the cyclization, but a greater influence on the procedure used to cleave the TBDMS group on the iminium ion intermediate (such as **3**, Scheme 2).

The indole **11** (entry 1, Table 2) and the nonaromatic enamine **16** (entry 2, Table 3) cyclized in 89% and 78% yield, respectively. The amide activation and cyclization requires heating at 40 °C during several hours for the indole **11**, compared to enamine **16**, which cyclized within 15 min at 0 °C. Because the only difference between these substrates is the nature of the tethered nucleophile, the difference in the reaction temperatures and time is indicative of the greater reactivity of aliphatic enamine relative the indole ring toward activated amide. It should be noted that activation of the indole tethered amide **11** with $POCl_3$ (entry 2, Table 2) was less efficient than the activation with Tf_2O (entry 1), as was observed for compound **37** (Table 1, entries 1 and 6).[26]

Comparison between Amides and Lactams. We compared the cyclization of identical nucleophilic moieties tethered to either aliphatic amides or butyrolactams. For the 5-*exo* cyclization of silyl enol ethers (entries 4 and 9, Table 2), the yield is much higher with the aliphatic amide (85 89%) than with the lactam (29 57%), whereas this order is reversed for the 6-*exo*

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(24) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(25) (a) For allylsilanes, the yields are reported for their cyclization and reduction. Attempts to hydrolyze the , -unsaturated iminium ion (such as **5**, Scheme 1) after cyclization gave inseparable mixtures of , - and , -enones. The reduction of the same iminium was also a lot cleaner than the hydrolysis. (b) For silyl enol ethers, the yields are reported for their cyclization and hydrolysis. (c) For aldehydic enamines, which are unstable and could not be isolated, the yields are reported for their formation and cyclization. Hydrolysis of the resulting vinylogous amidinium ions (such as **4**, Scheme 2) was not necessary because they were easily isolated and characterized.

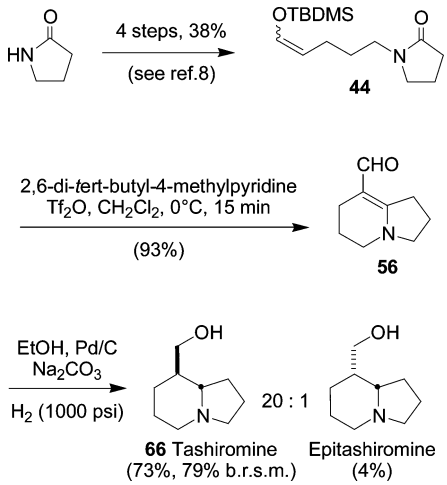
(26) The intermediate vinylogous amidinium ion was characterized by ^1H NMR spectroscopy prior to hydrolysis (see the Supporting Information).

(entries 6 and 10, respectively) and the 6-*endo* cyclizations (entries 12 and 15) . For both amides and lactams, as expected, 5-*endo* cyclizations are difficult but possible (39% and 29% yield, entries 11 and 14, respectively), showing the high reactivity of activated amides toward the -nucleophiles we used.

We also demonstrated that a tertiary amide (entry 4, Table 2) gives a much higher yield of enaminal than does a secondary amide (entry 3). The latter was not as easy to activate cleanly, and the nucleophilic addition of silyl enol ether was not as efficient. The activated secondary amide being a neutral imidate, it was anticipated that this imidate would be less reactive that the parent iminium ion from activation of tertiary amide.[27] When we compared the formamide **42** (entry 13, Table 2) to the corresponding acetamide **32** (entry 12) and lactam **44** (entry 15), the resulting enaminals **54**, **53**, and **56** respectively were obtained in similar yields (63%, 71%, and 73%, respectively) with the Pyr HF quench. This suggests a low influence of the iminium congestion in the cyclization step. However, when looking at the same entries but with the NaOH quench, there are large variations in the isolated yields (78% of **54**, 34% of **53**, and 93% of **56**). The ease of hydrolysis may explain the better yield for the formation of adduct **54** (78%, entry 13) over **53** (34%, entry 12), but we do not have a clear explanation for the high yield of **56** (93%). Finally, when we compare *N*,*N*-dibenzylamide **58** (74% yield, entry 1, Table 3) with *N*,*N*-diethylamide **16** (78% yield, entry 2), the nature of the alkyls on the amide nitrogen does not seem to have a large influence on the cyclization yield.

Application to the Synthesis of ( )-Tashiromine. Tashiromine (**66**) is an indolizidine alkaloid isolated in 1990 from the stems of a leguminous plant *Maackia tashiroi*, a deciduous shrub of subtropical Asia.[28] Six syntheses have been reported to date.[29] In our synthesis, we make use of the 6-*endo* cyclization of a TBDMS enol ether onto the activated butyrolactam **44**[8] to generate the bicyclic core of ( )-tashiromine in 93% yield. Upon treatment of the enaminal **56** with H_2 and Pd on carbon in the presence of Na_2CO_3,[30] a 20:1 mixture of ( )-tashiromine (**66**) and ( )-epitashiromine was obtained in 73% yield (or 79% yield, based on recovered starting material, Scheme 9). Because the *syn*-addition of hydrogen to the enaminal **56** alkene should lead to ( )-epitashiromine, we think that once the alkene in **56** is hydrogenated, a Na_2CO_3 catalyzed epimerization to the remaining aldehyde is faster than the hydrogenation of that aldehyde. The epimerization prior to the aldehyde reduction places the formyl group in the thermodynamic equatorial orientation. The synthesis of ( )-tashiromine was thus accomplished in 6 steps with an overall yield of 26%, which compares favorably to previously reported syntheses.[29] This expeditious synthesis is a prelude to the potential of amide activation and nucleophilic cyclization for the total synthesis of alkaloids.

SCHEME 9. Synthesis of ( )-Tashiromine



Conclusions

We demonstrated for the first time that activated amides could be trapped with tethered nonaromatic carbon nucleophiles in good to excellent yields. We showed that silyl enol ethers, enamines, and allylsilanes are compatible with amide activation and are the most efficient and well-suited nucleophiles for adding to the resulting iminium ion. Tashiromine is an example of the alkaloids that are accessible by the new monocyclizations we developed. We also confirmed that the species in solution after cyclization are iminium ions, whatever nucleophile is used for the cyclization. This is highly encouraging for the pursuit of our work toward our planned bis-cyclization strategy. The latter will furthermore open applications to the synthesis of polycyclic alkaloids. The results will be reported in due course.

Experimental Section

4-Methyl-3,4-dihydro-2*H*-cyclopenta[*b*]indol-1-one (45). Activation with $POCl_3$: To a solution of the amide **11** (100 mg, 0.390 mmol) in toluene (3.9 mL) at room temperature was added $POCl_3$ (43 L, 0.46 mmol). The mixture was then heated to reflux and kept at that temperature overnight. The dark mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to yield the iminium chloride salt intermediate as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) 7.63 (d, *J* 7.5 Hz, 1H), 7.28 (d, *J* 7.5 Hz, 1H), 7.16 (t, *J* 7.5 Hz, 1H), 7.07 (t, *J* 7.5 Hz, 1H), 4.14 (q, *J* 7.5 Hz, 2H), 3.89 3.82 (m, 5H), 3.73 3.72 (m, 2H), 3.43 3.40 (m, 2H), 1.58 (t, *J* 7.5 Hz, 3H), 1.49 (t, *J* 7.5 Hz, 3H); MS (*m*/*z*) 240 (M). The crude iminium salt was dissolved in a 1:1 solution of THF (2 mL) and 3 N NaOH (2 mL) and allowed to stir at room temperature overnight. After hydrolysis, most of the THF was removed by evaporation under reduced pressure. The resulting aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:98 MeOH EtOAc) to give 60 mg (78%) of pure **45** as a solid. **Activation with Tf_2O:** To a solution of the amide **11** (100 mg, 0.390 mmol) in dichloromethane (3.9 mL) at room temperature was added 4-(*N*,*N*-dimethylamino)pyridine (47 mg, 0.39 mmol), followed by Tf_2O (130 L, 770 mol). The solution was stirred at room temperature for 2 h, then was heated to reflux overnight. The reaction was worked up and purified as described in the $POCl_3$ activation method (vide supra) to give 64 mg (89%) of pure **45** as a solid.[31]

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1,2,3,5,6,7-Hexahydroindolizine-8-carbaldehyde (56). Tf_2O (33 μL, 0.19 mmol) was added dropwise to a solution of **44**[8] (50 mg, 0.18 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (40 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) at 0 °C, then the reaction mixture was stirred at 0 °C during 20 min. **Pyr·HF quench:** a prepared solution of Pyr·HF/pyridine/THF (4:5:20, 0.11 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. NaOH (1 N) was added, layers were separated, and the aq phase was extracted with CH_2Cl_2. Organic phases were combined, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (basic alumina, 100:2 EtOAc−MeOH) to give pure **56** as a yellowish oil. **NaOH quench:** the reaction mixture was concentrated by using a nitrogen flow, then THF (2 mL) and 1 N NaOH (2 mL) were added and the mixture was vigorously stirred overnight at room temperature. THF was evaporated under reduced pressure and the aq phase was extracted with CH_2Cl_2. The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (basic alumina, 100:2 EtOAc−MeOH) to give 25 mg (93%) of pure **56** as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 3.45 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 5.5 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H), 2.33 (t, J = 5.5 Hz, 2H), 2.05 (qi, J = 7.0 Hz, 2H), 1.83 (qi, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 164.4, 103.6, 53.4, 45.2, 28.5, 20.8, 20.6, 17.7; IR (film) ν 2939, 1577, 1438, 1108 cm^{-1}; HRMS (EI) calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.0994.

***(E)*-*N*,*N*-Dibenzyl-*N*-[2-(*N*′-methyl-*N*′-phenylaminomethylene)-cyclopentylidene]ammonium Trifluoromethanesulfonate (60).** Molecular sieves (4 Å, 600 mg) were added to a solution of **15**[8] (200 mg, 0.647 mmol) in $CHCl_3$ (5.0 mL) at 20 °C. *N*-Methylaniline (0.17 mL, 1.6 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. Conversion of **15** to the enamine **58** was followed by ^{1}H NMR of 0.1 mL aliquots sampled from the heterogeneous reaction mixture and diluted with $CDCl_3$ in an NMR tube.[32] The reaction mixture was cooled to 0 °C, then ^{i}Pr$_2$NEt was added (0.32 mL, 1.86 mmol), followed by a dropwise addition of Tf_2O (0.29 mL, 1.86 mmol) over 15−20 min. The reaction mixture was stirred for 15 min at 0 °C, then allowed to warm to room temperature and filtered on Celite (CH_2Cl_2 washing). The clear orange filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, 2:5:100 AcOH−MeOH−CH_2Cl_2) affording 254 mg (74%) of pure **60** as an amorphous semisolid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.48−6.97 (m, 15H), 5.10 (br s, 4H), 4.48 (br s, 3H), 3.45 (s, 2H), 2.99 (t, J = 7.5 Hz, 2H), 1.70 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 186.3, 158.6, 148.8, 140.0, 135.2, 133.9, 133.2, 132.4, 132.0, 128.7, 110.3, 65.3, 55.4, 41.2, 36.6, 26.3; IR (film) ν 3032, 2950, 2867, 1608, 1541, 1495, 1262, 1149, 1031 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{28}N_2^+$ (M^+) 380.2252, found 380.2246.

8-Ethylidene-2,3,5,6,7,8-hexahydro-1*H*-indolizinylium Trifluoromethanesulfonate (65). Tf_2O (77 μL, 0.46 mmol) was added dropwise to a solution of **36** (100 mg, 0.42 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (95 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After 20 min at 0 °C, the resulting mixture was allowed to warm to room temperature over 2 h, stirred overnight, then concentrated. 1,2-Dichloroethane (4 mL) was added and the solution was heated to reflux for 15 h, then was allowed to cool to room temperature and concentrated. The crude material was purified by flash chromatography (silica gel, 2:5:100 AcOH−MeOH−CH_2Cl_2) to afford 88 mg (70%) of pure **65** as a yellowish semisolid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (q, J = 7.0 Hz, 1H), 4.28 (t, J = 7.5 Hz, 2H), 3.81 (br t, J = 6.0 Hz, 2H), 3.37 (t, J = 7.5 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 2.33 (qi, J = 7.5 Hz, 2H), 2.10 (qi, J = 6.0 Hz, 2H), 2.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.8, 149.9, 128.0, 60.6, 48.0, 33.7, 20.4, 20.0, 18.2, 15.7; IR (film) ν 2966, 1641, 1260, 1156, 1029 cm^{-1}; MS (EI) *m*/*z* (rel %) 149 (70) [M^+], 148 (100) [M^+ − H], 122 (25); HRMS (EI) calcd for $C_{10}H_{15}N$ (M^+) 149.1204, found 149.1194.

(±)-Tashiromine (66). Pd/C (10%, 37 mg, 0.034 mmol) was added to a solution of **56** (48 mg, 0.32 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) in EtOH (99%, 4 mL) in a hydrogenation bomb. The bomb was purged with H_2 (3×) then filled with H_2 (1000 psi) and the solution was stirred for 24 h ar room temperature, followed by filtration on Celite (EtOAc washings). The filtrate was concentrated, then resubmitted to the same hydrogenation conditions (37 mg of 10% Pd/C, 36 mg of Na_2CO_3, 4 mL of EtOH, 1000 psi of H_2) at room temperature for 72 h. The reaction mixture was filtered on Celite (EtOAc washings) and the filtrate was concentrated. The crude material was purified by flash chromatography (basic alumina, 50:1 CH_2Cl_2−MeOH) to give 42 mg of a 20:1:2 inseparable mixture of (±)-tashiromine (**66**) (73%, 79% corrected), recovered starting material **56**, and (±)-epitashiromine (4%), respectively, as a yellowish oil. The characterization of a small amount of separated pure (±)-tashiromine corresponds to the one previously reported.[29e]

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Supporting Information Available: Experimental procedures for compounds **9**−**13**, **17**, **18**, **20**−**22**, **25**−**32**, **36**, **38**, **46**, **48**, **49**, **51**−**53**, **61**, **62**, and **64**, as well as ^{1}H and ^{13}C NMR spectra for compounds **10**−**13**, **17**−**22**, **25**−**32**, **36**, **38**, **46**, **48**, **49**, **51**−**53**, **61**, **62**, **64**, and **65**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The characterization is identical with the one reported for the same compound, but prepared through another route. See: (a) Bergman, J.; Baeckvall, J. E. *Tetrahedron* **1975**, *31*, 2063. (b) Gardette, D.; Gramain, J. C.; Lepage, M. E.; Troin, Y. *Can. J. Chem.* **1989**, *67*, 213.

(32) Ratios were determined from the characteristic signal for the protons α to the amide carbonyl of **14** and **58** appearing at 2.18 ppm (4H) versus the overlapping multiplets at 1.7−1.6 ppm accounting for a total of 6H (4H, β and γ to the amide carbonyl, in **15**, and 2H β to the amide carbonyl in **58**).