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Versatile One-Pot Reductive Alkylation of Lactams/Amides via Amide Activation: Application to the Concise Syntheses of Bioactive Alkaloids (±)-Bgugaine, (±)-Coniine, (+)-Preussin, and (−)-Cassine

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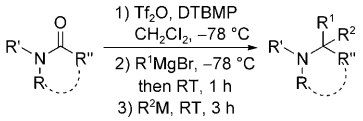
Efficiency is the central goal in organic synthesis.[1] Towards this goal, the development of one-pot multicomponent reactions[2] and step-economy synthesis[3] constitute two valuable approaches. In this context, we have recently reported the first general one-pot method for the transformation of lactams and amides into the corresponding *tert*-alkylamines[4] by bis-reductive alkylation with different organometallic reagents (Scheme 1).[4a]



Scheme 1. Tf_2O-Activated bis-reductive alkylation of lactams and amides. Tf_2O = Triflic anhydride; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

α-Substituted amines (*sec*-alkylamines), especially α-substituted pyrrolidines, piperidines and related ring systems, are key structural features found in many bioactive alkaloids and pharmaceutically relevant molecules.[5] For example, (−)-irniine (**1**) and (−)-bgugaine (**2**) (Figure 1) are alkaloids isolated from the tubers of *Arisaum vulgare*, which show antibacterial activity against Gram-positive bacteria and antimycotic activity against some *Candida* and *Cryptococcus* strains;[6a] bgugaine (**2**) was also shown to be a strong hepatotoxin in rat and human liver cell cultures;[6b] (+)-coniine (**3**) is one of the major toxic alkaloids present in poison hemlock;[7] (+)-preussin (**4**) is a potent antifungal agent isolated from fermentation broths of *Preussia sp.* and *Aspergillus ochraceus*.[8] Moreover, a number of α,α′-disubstituted 3-piperidinol alkaloids, such as (−)-cassine (**5**), (−)-spectaline (**6**), (+)-azimic acid (**7**), and (+)-carpamic acid (**8**), have been isolated, and many of them showed important biological activities.[5,9] As a consequence, numerous synthetic methods have been developed for the syntheses of such ring systems.[10] Among them, those based on the reductive alkylation of lactams are quite attractive due to their flexibility and versatility (Scheme 2).

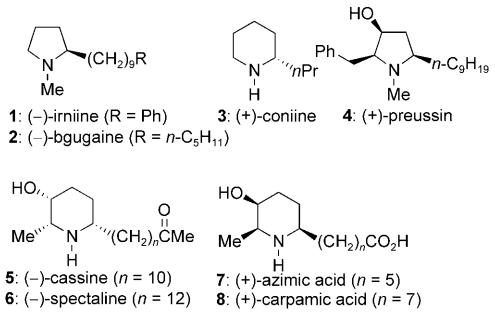
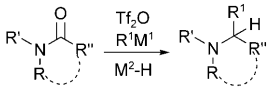


Figure 1. Selected naturally occurring α-substituted/α,α′-disubstituted pyrrolidine and piperidine alkaloids.



Scheme 2. General one-pot transformation of lactams/amides into the corresponding α-alkylated amines.

For the transformation of a lactam/amide into the corresponding α-substituted amines, two approaches can be envisioned, namely, mono-addition of an organometallic reagent followed by a chemoselective reduction,[11–13] and partial reduction by a hydride followed by a chemoselective organometallic reagent addition.[14] While both approaches have been used in the syntheses of alkaloids, they are limited to either special chelating substrates[11] or bicyclic lactams.[12,13] Noteworthy is that, to the best of our knowledge, only one case involved the transformation of an amide into the corre-

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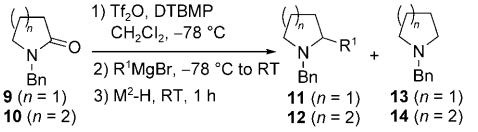
sponding α-substituted amine.[13a] Other drawbacks associated with some of the methods are low yields,[12b,c] epimerization at α-position,[12j] or use of excess of highly toxic $NaBH_3CN$ as the reducing agent.[11,12d,e] As a result, multistep transformations using either thioamides,[14c,15] lactim ethers,[16] *N*-*tert*-butyl formamidines,[17] vinyl triflates,[18] or *N*-acyl/*N*-alkoxycarbonyl derivatives[19–21] remain the most reliable and widely adapted methods. Moreover, many α-amidoalkylation methods are limited to silylated nucleophiles.[19]

As a continuation of our interest in the development of simple and efficient synthetic methodology,[4a,b] we now report a direct and versatile one-pot method for the transformation of lactams and amides into the corresponding α-substituted amines by the reductive alkylation of lactams/amides with Grignard reagents (Scheme 2), and the application of this methodology to the concise syntheses of (±)-bgugaine (**2**), (±)-coniine (**3**), (+)-preussin (**4**), and (−)-cassine (**5**).

To achieve the required one-pot reaction under mild conditions, a triflic anhydride (Tf_2O)/2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) combination[22] was selected as the amide activating system with Grignard reagents as alkylating agents and lithium aluminum hydride ($LiAlH_4$) as a reducing agent. It was found that when a CH_2Cl_2 solution of lactam **9** (1.0 equiv) and DTBMP (1.2 equiv) was treated successively with 1.2 equiv of Tf_2O (−78 °C, 45 min), 1.0 equiv of ethylmagnesium bromide in Et_2O (RT, 1 h), and 3.0 equiv of $LiAlH_4$ (RT, 1 h), the desired 2-ethylpyrrolidine **11a** was obtained in 82% yield, along with 8% yield of amine **13** (Table 1, entry 1). Following the same procedure,

Table 1. Tf_2O-Activated one-pot reductive alkylation of lactams.



Entry	Substrate	R^1MgBr	M^2-H	Product (Yield/%)[a]
1	**9**	EtMgBr	$LiAlH_4$	**11a** (82); **13** (8)
2	**9**	*n*BuMgBr	$LiAlH_4$	**11b** (79); **13** (10)
3	**9**	BnMgBr	$LiAlH_4$	**11c** (69); **13** (19)
4	**9**	PhMgBr	$LiAlH_4$	**11d** (58); **13** (26)
5	**10**	EtMgBr	$LiAlH_4$	**12a** (72) ; **14** (16)
6	**10**	*i*PrMgBr	$LiAlH_4$	**12b** (68); **14** (20)
7	**10**	BnMgBr	$LiAlH_4$	**12c** (62); **14** (23)
8	**9**	EtMgBr	$NaBH_4$	**11a** (71); **13** (8)

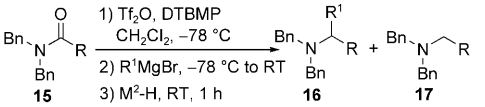
[a] Isolated yield.

the reactions of lactam **9** with *n*-butyl-, benzyl-, and phenyl-Grignard reagents gave the corresponding pyrrolidines **11b–d** in 58–79% yield (Table 1, entries 2–4). Similar results were obtained with lactam **10**, which provided the corresponding piperidines **12a–c** in good yields (Table 1, entries 5–7).

Similarly, the reductive alkylation of amides proceeded smoothly to give the desired products in high yields (Table 2, entries 1–3). It is noteworthy that $LiAlH_4$ can also be replaced by $NaBH_4$, which afforded the desired products in comparable yields (Table 1, entry 8 and Table 2, entry 4).

To demonstrate the synthetic utility of this one-pot method, the syntheses of bioactive alkaloids (±)-bgugaine (**2**),[23] (±)-coniine (**3**),[24] (+)-preussin (**4**),[25] and (−)-cassine (**5**)[26] were undertaken.

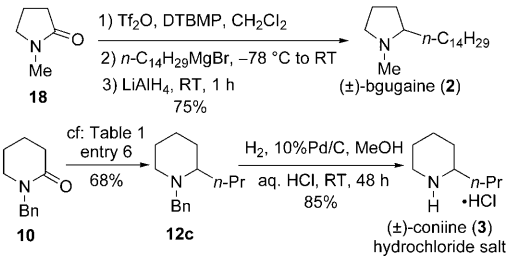
Table 2. Tf_2O-Activated one-pot reductive alkylation of amides.



Entry	Substrate	R^1MgBr	M^2-H	Product (Yield/%)[a]
1	**15a** (R = Me)	EtMgBr	$LiAlH_4$	**16a** (78); **17a** (13)
2	**15a** (R = Me)	*i*PrMgBr	$LiAlH_4$	**16b** (73); **17a** (9)
3	**15b** (R = Ph)	EtMgBr	$LiAlH_4$	**16c** (81); **17b** (10)
4	**15b** (R = Ph)	EtMgBr	$NaBH_4$	**16c** (80); **17b** (7)

[a] Isolated yield.

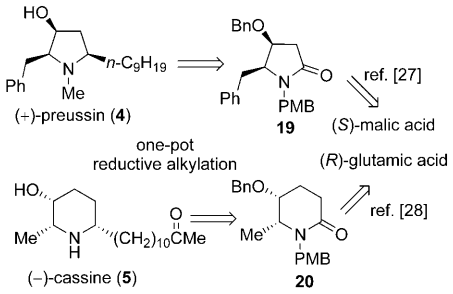
The syntheses of (±)-bgugaine (**2**) and (±)-coniine (**3**) are illustrated in Scheme 3. Using the general procedure, reductive *n*-tetradecylation of commercially available *N*-methylpyrrolidin-2-one (NMP, **18**) produced (±)-bgugaine (**2**) in 75% yield. Catalytic hydrogenation of amine **12c**, obtained from the reductive *n*-propylation of lactam **10** (Table 1, entry 6), gave coniine (**3**), isolated as its hydrochloride salt in 85% yield. The physical and spectral data of the synthetic products are in accordance with those reported for (±)-bgugaine (**2**)[23d] and (±)-coniine (**3**),[24b] respectively.



Scheme 3. Concise syntheses of (±)-bgugaine (**2**) and (±)-coniine (**3**).

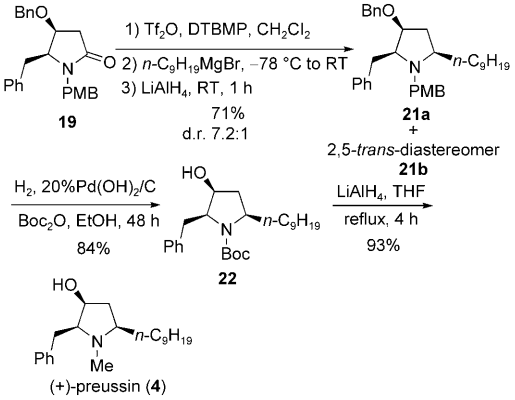
Encouraged by these results, we then focused on the stereoselective total syntheses of (+)-preussin (**4**) and (−)-cassine (**5**). Our retrosynthetic analysis is outlined in Scheme 4. For the key one-pot reductive alkylations of lactams **19** and **20**, two issues had to be addressed, namely, diastereoselectivity and the use of a functionalized Grignard reagent. Lactams **19** and **20** are easily available from (*R*)-glutamic acid and (*S*)-malic acid, respectively, by the methods we have reported previously.[27,28]

For the synthesis of (+)-preussin (**4**), the known lactam (4*S*,5*S*)-**19**[27] was subjected to reductive alkylation with *n*-nonylmagnesium bromide to give an inseparable mixture of diastereomers **21a** and **21b** in 71% combined yield, with a



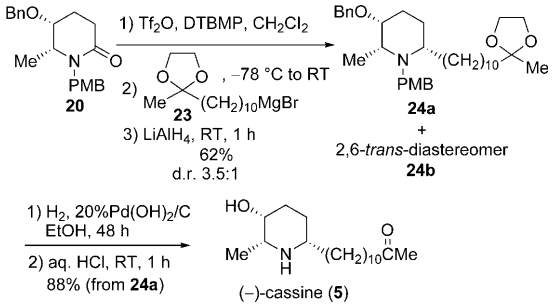
Scheme 4. Retrosynthetic analysis of (+)-preussin (**4**) and (−)-cassine (**5**).

cis/*trans* ratio of 7.2:1 (Scheme 5). The *cis*/*trans* ratio was determined by HPLC. The stereochemistry of the major product was confirmed by its ultimate conversion into (+)-preussin (**4**). To introduce the *N*-methyl group, the diastereomeric mixture of pyrrolidine **21** was subjected to one-pot debenzylation–urethanation [H_2, 1 datm, 20% $Pd(OH)_2$/C, $(Boc)_2O$, EtOH, RT, 48 h], and the *N*-*tert*-Boc derivative **22** was obtained in 84% yield. The *N*-Boc group was then converted into the corresponding *N*-methyl group by reduction with $LiAlH_4$, which afforded (+)-preussin (**4**) {$[\alpha]_D^{20} = +22.3$ (c = 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{20} = +22.0$ (c = 1.0, $CHCl_3$)} in 93% yield. The ^1H and ^{13}C NMR spectral data of our synthetic product are in good agreement with those reported.[8]



Scheme 5. Total synthesis of (+)-preussin (**4**).

We next addressed the synthesis of (−)-cassine (**5**). To this end, (5*R*,6*R*)-lactam **20**, prepared following essentially the procedure described for its enantiomer,[28] was subjected to the one-pot reductive alkylation reaction by successive treatment with Tf_2O/DTBMP, Grignard reagent **23**,[29] and $LiAlH_4$, which afforded a mixture of separable diastereomers **24a** and **24b** in 3.5:1 ratio with a 62% combined yield (Scheme 6). The stereochemistry of the major diastereomer was confirmed by its ultimate conversion into (−)-cassine (**5**). Deprotection of *O*-Bn and *N*-PMB in **24a** under catalytic hydrogenolytic conditions [H_2, 1 atm, 20% $Pd(OH)_2$/C, EtOH, RT, 48 h], followed by treatment of the resultant crude product with aqueous HCl and neutralization, led to (−)-cassine (**5**) {m.p. 56–57 °C; lit.[30] m.p. 57–58 °C; $[\alpha]_D^{20} = -1.2$ (c = 0.5, EtOH); $[\alpha]_D^{20} = -15.4$ (c = 0.5, $CHCl_3$); lit.[30] $[\alpha]_D^{20} = -0.6$ (c = 8.0, EtOH)} in 88% yield. The ^1H and ^{13}C NMR spectral data of our synthetic product are in good agreement with those reported.[26e]



Scheme 6. Total synthesis of (−)-cassine (**5**).

In summary, a direct and versatile method for the one-pot reductive alkylation of lactams/amides with Grignard reagents has been developed. This method opens a direct entry to α-alkylated amines. The power of the methodology is demonstrated by the concise syntheses of bioactive alkaloids (±)-bgugaine (**2**), (±)-coniine (**3**), (+)-preussin (**4**), and (−)-cassine (**5**). The syntheses of latter two alkaloids allow the demonstration of the diastereoselectivity of the method. Further application of this method to the total synthesis of other alkaloids is under investigation.

Experimental Section

General procedure for the reductive alkylation of lactams/amides: Tf_2O (1.2 equiv) was added dropwise to a cooled (−78 °C) solution of a lactam/amide (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.2 equiv) in CH_2Cl_2 and the resultant mixture was stirred at −78 °C for 45 min. A solution of RMgBr (1.0 equiv) in Et_2O was added dropwise to the resultant mixture. The mixture was allowed to warm slowly to RT and stirred for 1 h. Then $LiAlH_4$ (3.0 eq) or $NaBH_4$ (3.0 equiv) was added in one portion. After stirring for 1 h, the reaction was quenched by careful addition of a 20% NaOH solution. After filtration, the filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 to afford the desired amine. Further experimental details can be found in the Supporting Information.

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Keywords: alkaloids · amide activation · reduction · synthetic methods

[1] For selected reviews, see: a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) C. J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202.

[2] For selected reviews, see: a) Multicomponent Reactions, (Eds.: J.-P. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; b) "Multicomponent reactions: Tetrahedron Symposium-in-Print No. 114", *Tetrahedron* **2005**, *61*, 11309–11519; c) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; d) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463–472.

[3] a) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25–31; b) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 765–769; c) P. A. Wender, B. L. Miller in *Organic Synthesis: Theory and Applications, Vol. 2* (Ed.: T. Hudlicky), JAI, Greenwich, **1993**, pp. 27–66; d) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505–7511.

[4] a) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem.* **2010**, *122*, 3101–3104; *Angew. Chem. Int. Ed.* **2010**, *49*, 3037–3040. For a Tf_2O-activated reduction of amides amines, see: b) S.-H. Xiang, J. Xu, H.-Q. Yuan, P.-Q. Huang, *Synlett* **2010**, 1829–1832. For a review on the synthesis of cyclopropylamines from amides by the Kulinkovich–de Meijere reaction, see: c) A. de Meijere, S. I. Kozhushkov, A. I. Savchenko, *J. Organomet. Chem.* **2004**, *689*, 2033–2055. For the one-pot bis-reductive alkylation of *N*,*N*-dialkylformamides, see: d) O. Tomashenko, V. Sokolov, A. Tomashevskiy, H. A. Buchholz, U. Welz-Biermann, V. Chaplinski, A. de Meijere, *Eur. J. Org. Chem.* **2008**, 5107–5111. For indirect methods via thioamides, see: e) T. Murai, R. Toshio, Y. Mutoh, *Tetrahedron* **2006**, *62*, 6312–6320; f) A. Agosti, S. Britto, P. Renaud, *Org. Lett.* **2008**, *10*, 1417–1420.

[5] For a review on piperidine alkaloids, see: a) M. Schneider in *Alkaloids: Chemical and Biochemical Perspectives, Vol. 10* (Ed.: S. W. Pelletier), Elsevier Science, Oxford, **1996**, pp. 155–299. For a review on pyrrolidine alkaloids, see: b) H. Takahata, T. Momose, in *The Alkaloids, Vol. 44* (Ed.: G. A. Cordell), Academic Press, San Diego, CA, **1993**, Chapter 3. For reviews on pyrrolidine and piperidine alkaloids, see: c) J. P. Michael, *Nat. Prod. Rep.* **1999**, *16*, 675–696; d) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556–1575.

[6] a) A. Melhaoui, M. Mallea, A. Jossang, B. Bodo, *Nat. Prod. Lett.* **1993**, *2*, 237–242; b) N. Rakba, A. Melhaoui, P. Loyer, J. G. Delcros, I. Morel, G. Lescoat, *Toxicol. Lett.* **1999**, *104*, 239–248.

[7] a) T. A. López, M. S. Cid, M. L. Bianchini, *Toxicon* **1999**, *37*, 841–865; b) S. T. Lee, B. T. Green, K. D. Welch, J. A. Pfister, K. E. Panter, *Chem. Res. Toxicol.* **2008**, *21*, 2061–2064.

[8] a) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, J. Onishi, R. Monaghan, *J. Antibiot.* **1988**, *41*, 1774–1779; b) J. H. Johnson, D. W. Phillipson, A. D. Kahle, *J. Antibiot.* **1989**, *42*, 1184–1185.

[9] a) P. Sansores-Peraza, M. Rosado-Vallado, W. Brito-Loeza, G. J. Mena-Rejón, L. Quijano, *Fitoterapia* **2000**, *71*, 690–692; b) V. da S. Bolzani, A. A. L. Gunatilaka, D. G. I. Kingston, *Tetrahedron* **1995**, *51*, 5929–5934; c) C. Viegas, Jr., D. H. S. Silva, M. Pivatto, A. de Rezende, I. Castro-Gambôa, V. S. Bolzani, M. G. Nair, *J. Nat. Prod.* **2007**, *70*, 2026–2028; d) C. Viegas, Jr., M. S. Alexandre-Moreira, C. A. M. Fraga, E. J. Barreiro, V. da Silva Bolzani, A. L. P. de Miranda, *Chem. Pharm. Bull.* **2008**, *56*, 407–412; e) N. G. Castro, R. S. Costa, L. S. B. Pimentel, A. Danuello, N. C. Romeiro, C. Viegas Jr., E. J. Barreiro, C. A. M. Fraga, V. S. Bolzani, M. S. Rocha, *Eur. J. Pharmacol.* **2008**, *580*, 339–349.

[10] For selected reviews on the stereoselective syntheses of pyrrolidines and piperidines, see: a) D. L. Comins, S. P. Joseph, *Adv. Nitrogen Heterocycl.* **1996**, *2*, 251–294; b) H.-P. Husson, J. Royer, *Chem. Soc. Rev.* **1999**, *28*, 383–394; c) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781–1813; d) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843–9873; e) N. Toyooka, H. Nemoto, *Drugs Future* **2002**, *27*, 143–158; f) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; g) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; h) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; i) M. A. Wijdeven, J. Willemsen, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2010**, 2831–2844.

[11] a) M. Schibagaki, H. Matushita, H. Kaneko, *Heterocycles* **1986**, *24*, 2315–2319; b) Y. Watanabe, H. Iida, C. Kibayashi, *J. Org. Chem.* **1989**, *54*, 4088–4097; c) T. Sato, S. Aoyagi, C. Kibayashi, *Org. Lett.* **2003**, *5*, 3839–3842.

[12] a) Y. C. Hwang, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 2719–2726; b) T. Shono, Y. Matsumura, K. Uchida, H. Kobayashi, *J. Org. Chem.* **1985**, *50*, 3243–3245; c) A. Satake, I. Shimizu, *Tetrahedron: Asymmetry* **1993**, *4*, 1405–1408; d) S. Nukui, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 398–404; e) D. L. Comins, X. Zheng, R. R. Goehring, *Org. Lett.* **2002**, *4*, 1611–1613; f) V. Gracias, Y. Zeng, P. Desai, J. Aube, *Org. Lett.* **2003**, *5*, 4999–5001; g) M. Katoh, H. Mizutani, T. Honda, *Tetrahedron Lett.* **2005**, *46*, 5161–5163; h) K. M. Goodenough, W. J. Moran, P. Raubo, J. P. A. Harrity, *J. Org. Chem.* **2005**, *70*, 207–213; i) B. B. Snider, J. F. Grabowski, *J. Org. Chem.* **2007**, *72*, 1039–1042; j) P. Ghosh, W. R. Judd, T. Ribelin, J. Aube, *Org. Lett.* **2009**, *11*, 4140–4142.

[13] An unsuccessful attempt at the reductive alkylation of a monocyclic lactam (*N*-methyl-2-piperidinine) has been noted in ref. 11b. For the only known example of the reductive alkylation of a monocyclic lactam, see: a) Y. C. Hwang, M. Chu, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 3885–3890. For a one-pot reductive alkynylation using alkynyl boranes, see: b) M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 1719–1722.

[14] For two successful examples, see: a) L. E. Overman, D. Lesuisse, M. Hashimoto, *J. Am. Chem. Soc.* **1983**, *105*, 5373–5379 (1-pentynylation); b) Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Koo, H.-S. Kim, *Angew. Chem.* **1999**, *111*, 3753–3755; *Angew. Chem. Int. Ed.* **1999**, *38*, 3545–3547 (ethylation). For a specific example, see: c) M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928.

[15] a) K. Shiosaki, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 1229–1239; b) W. J. Klaver, H. Hiemstra, W. N. Speckamp, *J. Am. Chem. Soc.* **1989**, *111*, 2588–2595; c) N. Toyooka, Y. Yoshida, Y. Yotsui, T. Momose, *J. Org. Chem.* **1999**, *64*, 4914–4919; d) P. Schär, P. Renaud, *Org. Lett.* **2006**, *8*, 1569–1571; e) H. Takahata, K. Takahashi, E.-C. Wang, T. Yamazaki, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1211–1214.

[16] a) O. Provot, J. P. Célérier, H. Petit, G. Lhommet, *J. Org. Chem.* **1992**, *57*, 2163–2166; b) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *Tetrahedron* **1993**, *49*, 8805–8826; c) G. Mehta, M. Praveen, *J. Org. Chem.* **1995**, *60*, 279–280.

[17] L. Gottlieb, A. I. Meyers, *Tetrahedron Lett.* **1990**, *31*, 4723–4726.

[18] For selected examples, see: a) J. Jiang, R. J. DeVita, G. A. Doss, M. T. Goulet, M. J. Wyvratt, *J. Am. Chem. Soc.* **1999**, *121*, 593–594; b) J. D. Ha, J. K. Cha, *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020.

[19] For recent reviews on the α-amidoalkylation via *N*-acyliminium ion intermediates, see: a) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368; b) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541. For a very recent example, see: c) M. A. Wijdeven, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron* **2010**, *66*, 5623–5636.

[20] For selected examples, see: a) A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228–234; b) G. D. Cuny, S. L. Buchwald, *Synlett* **1995**, 519–522; c) H. Yoda, H. Yamazaki, M. Kawauchi, K. Takabe, *Tetrahedron: Asymmetry* **1995**, *6*, 2669–2672; d) I. Collado, J. Ezquerra, C. Pedregal, *J. Org. Chem.* **1995**, *60*, 5011–5015; e) A. Kanazawa, S. Gillet, P. Delair, A. E. Greene, *J. Org. Chem.* **1998**, *63*, 4660–4663; f) W. Wang, J. Yang, J. Ying, C. Xiong, J. Zhang, C. Cai, V. J. Hruby, *J. Org. Chem.* **2002**, *67*, 6353–6360; g) C. E. Neipp, S. F. Martin, *J. Org. Chem.* **2003**, *68*, 8867–8878; h) P.-Q. Huang, T.-J. Wu, Y.-P. Ruan, *Org. Lett.* **2003**, *5*, 4341–4344; i) J. B. Brenneman, S. F. Martin, *Org. Lett.* **2004**, *6*, 1329–1331; j) J. B. Brenneman, R. Machauer, S. F. Martin, *Tetrahedron* **2004**, *60*, 7301–7314.

[21] For transformations via *N*-α-phenylsulphonyl derivatives, see: a) D. S. Brown, P. Clarreau, T. Hansson, S. V. Ley, *Tetrahedron* **1991**, *47*, 1311–1328; b) M. Ostendorf, S. van der Neut, F. P. J. T. Rutjes,

H. Hiemstra, *Eur. J. Org. Chem.* **2000**, 105–113; c) M. G. Moloney, T. Panchal, R. Pike, *Org. Biomol. Chem.* **2006**, *4*, 3894–3897.

[22] For selected examples on the use of Tf_2O as a powerful amide activator for a variety of transformations, see: a) A. B. Charette, P. Chua, *J. Org. Chem.* **1998**, *63*, 908–909; b) C. E. McDonald, A. M. Galka, A. I. Green, J. M. Keane, J. E. Kowalchick, C. M. Micklitsch, D. D. Wisnoski, *Tetrahedron Lett.* **2001**, *42*, 163–166; c) A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, *J. Am. Chem. Soc.* **2001**, *123*, 11829–11830; d) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592–4593; e) G. Bélanger, R. Larouche-Gauthier, F. Ménard, M. Nantel, F. Barabé, *J. Org. Chem.* **2006**, *71*, 704–712; f) Q.-L. Dong, G.-S. Liu, H.-B. Zhou, L. Chen, Z.-J. Yao, *Tetrahedron Lett.* **2008**, *49*, 1636–1640; g) S.-L. Cui, J. Wang, Y.-G. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 13526–13527.

[23] For the syntheses of bgugaine, see: a) M. S. Majik, P. S. Parameswaran, S. G. Tilve, *J. Chem. Res.* **2008**, 121–122; b) O. Miyata, S. Takahashi, A. Tamura, M. Ueda, T. Naito, *Tetrahedron* **2008**, *64*, 1270–1284; c) D. Enders, C. Thiebes, *Pure Appl. Chem.* **2001**, *73*, 573–578; d) H. Takahata, K. Ihara, M. Kubota, T. Momose, *Heterocycles* **1997**, *46*, 349–356; e) A. Jossang, A. Melhaoui, B. Bodo, *Heterocycles* **1996**, *43*, 755–766; f) D. Enders, C. Thiebes, *J. Indian Chem. Soc.* **1999**, *76*, 561–564.

[24] For recent asymmetric syntheses of coniine, see: a) J. Bourgeois, I. Dion, P. H. Cebrowski, F. Loiseau, A.-C. Bédard, A. M. Beauchemin, *J. Am. Chem. Soc.* **2009**, *131*, 874–875; b) S. M. Hande, N. Kawai, J. Uenishi, *J. Org. Chem.* **2009**, *74*, 244–253; c) S. Lauzon, F. Tremblay, D. Gagnon, C. Godbout, C. Chabot, C. Mercier-Shanks, S. Perreault, H. Desève, C. Spino, *J. Org. Chem.* **2008**, *73*, 6239–6250; d) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Org. Lett.* **2007**, *9*, 2473–2476; e) S. Fustero, D. Jimènez, J. Moscardó, S. Catalán, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283–5286; f) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, *128*, 9646–9647.

[25] For recent asymmetric syntheses of (+)-preussin, see: a) N. Gogoi, J. Boruwa, N. C. Barua, *Eur. J. Org. Chem.* **2006**, 1722–1725; b) F. A. Davis, J. Zhang, H. Qiu, Y. Wu, *Org. Lett.* **2008**, *10*, 1433–1436; c) M. B. Bertrand, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2353–2356; d) J. J. Caldwell, D. Craig, S. P. East, *ARKIVOC* **2007**, *XII*, 67–90. For a recent review, see: e) B. Basler, S. Brandes, A. Spiegel, T. Bach, *Top. Curr. Chem.* **2005**, *243*, 1–42.

[26] For recent asymmetric syntheses of (−)-cassine, see: a) G. Kim, N. Kim, *Tetrahedron Lett.* **2007**, *48*, 4481–4483; b) C. A. Leverett, M. P. Cassidy, A. Padwa, *J. Org. Chem.* **2006**, *71*, 8591–8601; c) C. Herdeis, P. Kuepper, S. Ple, *Org. Biomol. Chem.* **2006**, *4*, 524–529; d) M.-R. Tsai, B.-F. Chen, C.-C. Cheng, N.-C. Chang, *J. Org. Chem.* **2005**, *70*, 1780–1785; e) H. Makabe, L. K. Kong, H. Mitsura, *Org. Lett.* **2003**, *5*, 27–29.

[27] S.-H. Xiang, H.-Q. Yuan, P.-Q. Huang, *Tetrahedron: Asymmetry* **2009**, *20*, 2021–2026.

[28] a) L.-X. Liu, K.-J. Xiao, P.-Q. Huang, *Tetrahedron* **2009**, *65*, 3834–3841; b) D.-S. Yu, W.-X. Xu, L.-X. Liu, P.-Q. Huang, *Synlett* **2008**, 1189–1192.

[29] a) J. Oetting, J. Holzkamp, H. H. Meyer, A. Pahl, *Tetrahedron: Asymmetry* **1997**, *8*, 477–484; b) J. Jiang, C. Jiang, W. Yang, H. Zhen, F. Hung, Y. Cao, *Macromolecules* **2005**, *38*, 4072–4080.

[30] R. J. Highet, *J. Org. Chem.* **1964**, *29*, 471–474.

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