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S_N1-like Reactions of Bicyclic α-Amino Ethers with Sulfur, Nitrogen, and Carbon Nucleophiles. Synthesis of 1-Azabicyclo[3.2.2]nonanes Functionalized at Carbon C2 and C6 with Complete Stereocontrol

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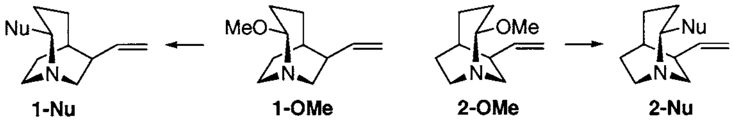
ABSTRACT



In the presence of nucleophiles, Lewis acid mediated cleavage of α-amino ethers derived from quincorine and quincoridine affords a variety of C2-substituted and C6-vinylated 1-azabicyclo[3.2.2]nonanes. These are enantiopure and are formed in S_N1-like reactions with complete stereocontrol. There is no leakage into 2-Nu en route to product 1-Nu or vice versa. Me_3SiCN provides new Strecker-type α-amino nitriles. In the presence of TTMPP–$BF_3 \cdot OEt_2$, the ketene acetal $Me_2C{=}C(OMe)OSiMe_3$ delivers enantiopure bicyclic β-amino acid esters.

The 1-azabicyclo[3.2.2]nonane moiety is encountered only rarely in nature[1] and has been accessible in the laboratory with some difficulty.[2] Substituted 1-azabicyclo[3.2.2]nonanes are of interest as chiral auxiliaries in asymmetric synthesis and act as 5-HAT receptor antagonists for the treatment of inflammatory and central nervous system disorders.[3]

Recent work has shown that bicyclic α-amino ethers **1-OMe** and **2-OMe** are readily prepared from quincorine and quincoridine,[4] respectively, in good yield (Scheme 1).[5] Both cage-expanded [3.2.2]azabicycles are enantiopure and contain four stereogenic centers including the 1*S*-configured basic bridgehead nitrogen. We now describe the Lewis acid assisted displacement of the α-methoxy group by carbon, nitrogen, and sulfur nucleophiles.

The solvent acetonitrile, which often serves as a solvent for generating carbocations, was unsatisfactory (Table 1,

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(1) For examples, see: (a) Nomofungin: Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717. (b) Communesins, Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.

(2) (a) Ruggles, C. J.; Halpern, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 5692. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183. (c) Vorob'eva, V. Ya.; Mikhlina, E. E.; Turchin, K. F. Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1970**, *8*, 1037. (d) Yanina, A. D.; Mikhlina, E. E.; Rubtsov, M. V. *Zh. Org. Khim.* **1966**, *2*, 1707. (e) Prelog, V.; Cerkovnikov, E. *Liebigs. Ann.* **1937**, *532*, 83.

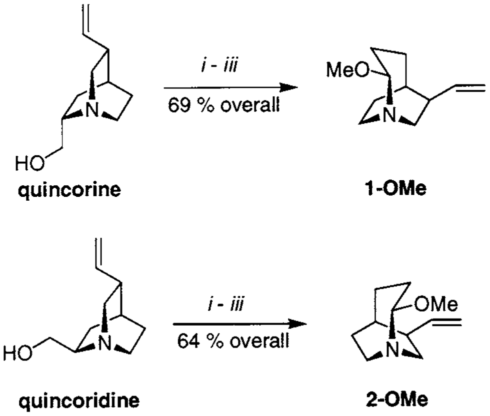
(3) (a) Lowe, J. A., III. PCT Int. Appl. WO 9215585, 1992. (b) Lowe, J. A., III; Drozda, S. E.; Snider, R. M.; Longo, K. P.; Rizzi, J. P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 921. (c) King, F. D.; Joiner, K. A. Eur. Pat. App. EP 214772, 1987 (US 4798829, 1986). (d) Mueller, R. A.; Partis, R. A.; Deason, J. R. Eur. Pat. Appl. EP 190684, 1986.

(4) Hoffmann, H. M. R.; Plessner, T.; von Riesen, C. *Synlett* **1996**, 690 and subsequent papers.

(5) Röper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1661.

10.1021/ol026342m CCC: $22.00

Scheme 1. Stereospecific Ring Expansion of Quincorine and Quincoridine to 1-Azabicyclo[3.2.2]nonanes[5] [a]



[a] (i) MsCl (1.3 equiv), NEt_3 (2.0 equiv), DCM, 0 °C → rt, 2 h; (ii) LiI, dioxane, 100 °C, 3 h; (iii) AgOBz, MeOH, 60 °C, 16 h.

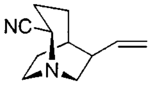
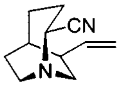
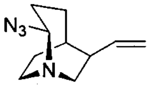
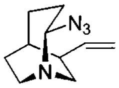
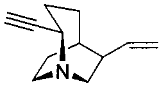
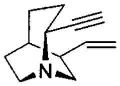
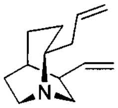
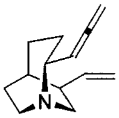
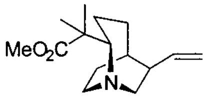
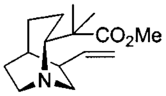
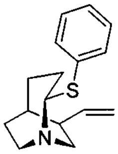
Table 1.

entry	nucleophile (equiv) Lewis acid (equiv)	solvent	*T* (°C)	yield[a] (%)
1	Me_3SiCN (2.5) $BF_3 \cdot OEt_2$ (1.0)	MeCN	−40 → rt	0
2	Me_3SiCN (2.5) $BF_3 \cdot OEt_2$ (1.5)	MeCN	−40 → rt	15[b]
3	Me_3SiCN (2.5) $BF_3 \cdot OEt_2$ (3.0)	MeCN	−40 → rt	26[c]
4	Me_3SiCN (4.0) $BF_3 \cdot OEt_2$ (1.1)	$MeNO_2$	−40 → rt	0[d]
5	Me_3SiCN (5.0) $BF_3 \cdot OEt_2$ (1.1)	DCM	−40 → rt	83

[a] Isolated yield. [b] 8 h, 72%. [c] 16 h. [d] 7 d, 25%, yield determined by gas chromatography.

entry 1), as was nitromethane, an iminium ion stabilizing solvent (Table 1, entry 4).[6] With an excess of $BF_3 \cdot OEt_2$, reaction of **1-OMe** with Me_3SiCN in acetonitrile provided the desired α-amino nitrile in only 15−26% yield (Table 1, entries 2 and 3). In contrast, reactions in less polar dichloromethane with $BF_3 \cdot OEt_2$ as Lewis acid[7] were promising and afforded trifunctional α-amino nitrile[8] **1-CN** in excellent chemical yield (83%) (Table 1, entry 5). Application of the condition in entry 5 to the trimethylsilyl azide as nucleophile was equally effective (Table 2, entries 3 and 4).

Table 2.

Entry	α-Amino ether	Condition[a]	Product	Yield [%]
1	**1-OMe**	A		83
2	**2-OMe**	A		68
3	**1-OMe**	A		81
4	**2-OMe**	A		75
5	**1-OMe**	B		39
6	**2-OMe**	B		70
7	**2-OMe**	C		48
8	**2-OMe**	A		24
9	**1-OMe**	D		66
10	**2-OMe**	D		70
11	**2-OMe**	A		59

[a] Key: reaction temperature, −40 °C → rt; (A) Me_3Si-nucleophile, $BF_3 \cdot OEt_2$, DCM; (B) $Bu_3SnC{\equiv}CH$, $BF_3 \cdot OEt_2$ ref. 15; (C) C_3H_5MgBr, $BF_3 \cdot OEt_2$, THF; (D) $Me_2C{=}C(OMe)OSiMe_3$, TTMPP−$BF_3 \cdot OEt_2$, DCM/MTBE (20:1).[14]

Following these initial experiments, we investigated a range of nucleophiles and the two substrates **1-OMe** and **2-OMe**. Pseudo-enantiomeric[9] α-amino ether, **2-OMe** derived from quincoridine reacted similarly and was fractionally less efficient than **1-OMe** (Table 2, entry 2). Furthermore, $Me_3Si{-}SPh$ provided **2-SPh** (59%, Table 2, entry 11).

However, carbon nucleophiles other than simple cyanide ion required further experimentation. Following a literature

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(6) For general aspects of preparative carbocation chemistry, see: (a) Yoshida, T., Suga, S. *Chem. Eur. J.* **2002**, *8*, 2651−2558. (b) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393; *Angew. Chem.* **1995**, *107*, 1519 (Nobel lecture). (c) *Methoden der Organischen Chemie, Houben-Weyl*; Hanack, M., Ed.; Thieme: Stuttgart, 1990; Vol. E19c. (d) Denmark, S. E.; Willson, T. M. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, 1989; pp 247−263.

(7) (a) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1984**, *25*, 3115. For a review on additions to *N*-acyliminium ions, see: (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082. See also: (c) Schroth, W.; Jahn, U. *J. Prakt. Chem.* **1998**, *340*, 287−299.

protocol, the allyl group was introduced by allylmagnesium bromide and $BF_3\cdot OEt_2$ (Table 2, entry 7).[10] Attempts to introduce the ethynyl moiety via Mg and Si chemistry were not successful. However, stannylated ethyne and $BF_3\cdot OEt_2$ furnished quincorine-derived **1-ethyne** (Table 2, entry 5) and also quincoridine-derived **2-ethyne** (Table 2, entry 6).[11] Reaction of **2-OMe** with propargyltrimethylsilane and $BF_3\cdot OEt_2$ furnished the pharmacologically interesting α-allenic amine **2-allene**[12] (Table 2, entry 8).

In an attempt to synthesize bicyclic *β*-amino acids, we treated silylated ketene acetal $Me_2C{=}C(OMe)OSiMe_3$ with α-amino ethers **1-OMe** and **2-OMe** under a variety of conditions including the standard protocol (Table 1, entry 5). No product was observed. Eventually, the reactions were repeated in the presence of TTMPP [tris(trimethoxyphenyl)-phosphine] (Figure 1) and $BF_3\cdot OEt_2$, which is a push−pull combination containing a highly nucleophilic phosphine and useful in Mukaiyama aldol reactions.[13] We were pleased to isolate both **1-ester** and **2-ester** containing a new quarternary carbon in a respectable 66% and 70% yield.[14]

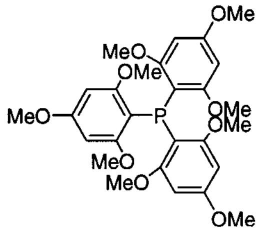


Figure 1. TTMPP.

The synthesis of *β*-amino acid ester **1-ester** (Table 2, entry 9) and **2-ester** (Table 2, entry 10) in enantiopure form is a test of the utility and efficiency of TTMPP−$BF_3\cdot OEt_2$ in this S_N1-like reaction. Unlike cyanide and azide ion, the silyl ketene acetal $Me_2C{=}C(OMe)OSiMe_3$ is more hindered for effecting the desired carbon−carbon bond formation.

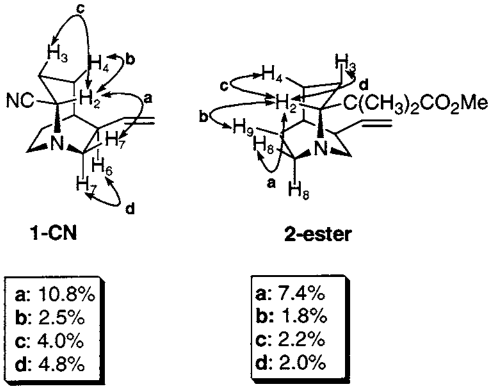
α-Amino ethers, which are trifunctional, with functionality other than vinyl at C6 (ethyl, ethynyl and cross-coupled ethynyls, oxo, ester) are also known.[5]

The configuration and conformation of 1-azabicyclo[3.2.2]-nonanes were determined by NMR and X-ray analysis. The configuration at C2 could be assigned by NOE interactions of proton H2, with neighboring syn-axial like protons: see interaction "a" in **1-CN** and **2-ester** (Figure 2).

Figure 2. X-ray structure of **2-SPh**.[16]

X-ray analysis for **2-SPh** showed the asymmetric unit to contain two conformers **A** and **B**, approximately related by a C_2 operation. Major differences are found for torsion angles N1−C2−S−Ph (−61.5 for **A** and −78.0 for **B**) and for C11−C10−C6−C7 (14.1 for **A** and 103.8 for **B**). Conformational mobility ("butterfly conformers") has also been observed for nomofungin[1a] and may be relevant to biological activity (Scheme 2).

Scheme 2. NOE of **1-CN** and **2-Ester**



Mechanistic Aspects. While reactions of carbocations are often difficult to control, especially with respect to stereochemistry, the configuration at carbon C2 is retained throughout the reaction. Equilibration between the postulated chiral cations **1**$^+$ and **2**$^+$ is not observed (Scheme 3).

Moreover, there is also remarkable stereocontrol of subsequent external nucleophilic attack, which proceeds

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(8) For a review on α-amino nitriles, see: (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359−373 and references therein. (b) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org.* **1998**, *1*, 63. (c) Suginome, M.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **2002**, 1392.

(9) Replacement of the vinyl group by hydrogen generates enantiomers. The term *pseudo-enantiomer* is used routinely for related pairs of *Cinchona* alkaloids, e.g., quinine and quinidine.

(10) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

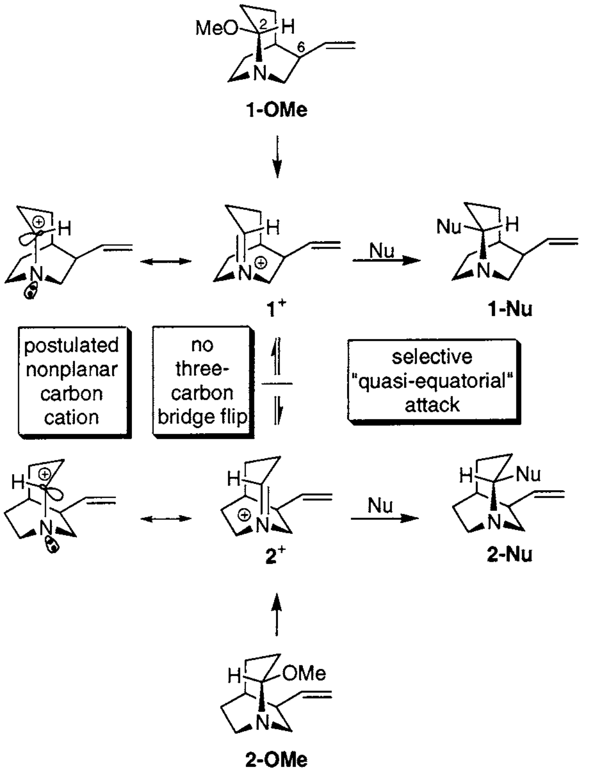
(11) (a) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (b) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310.

(12) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 367.

(13) Hartung, I. V.; Hoffmann, H. M. R. Submitted for publication. TTMPP is also sufficiently basic (pK_a 11.2) for desilylation of ketene acetal in situ.

(14) A solution of α-amino ether **1-OMe** (77 mg, 0.43 mmol) and TTMPP (46 mg, 20 mol %) in absolute DCM/MTBE (3 mL, 20:1) was cooled to −40 °C. The ketene acetal (0.22 mL, 1.06 mmol, 2.5 equiv) and then $BF_3\cdot OEt_2$ (66 *μ*L, 0.51 mmol, 1.2 equiv) were added. The mixture was allowed to warm to room temperature. After being stirred for 3 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, evaporated, and purified by column chromatography (PE/MTBE 1:1) to furnish **1-ester** (66%, 70 mg).

Scheme 3. Distinct Bridgehead Iminium Ions **1**$^+$ and **2**$^+$ and Their Stereospecific Capture by Nucleophiles



quasi-equatorially. The pyramidalized cationic intermediate can be regarded as a strained nonplanar cyclic iminium ion,[17] in a formal violation of the Bredt rule. These preparative findings mirror earlier results of Scheme 1, where both quincorine and quincoridine fully retained their stereochemical integrity, giving the ring expanded α-amino ethers **1-OMe** and respectively, **2-OMe**. The energy barrier to rotation and bridge flipping of our bridgehead iminium ions must be substantial.[18]

In conclusion, bicyclic α-amino ethers **1-OMe** and **2-OMe** have been elaborated by Lewis acid promoted reactions with a variety of nucleophiles in stereocontrolled fashion. The resulting azabicyclics are enantiopure and readily available as pseudo-enantiomeric pairs. α-Amino nitriles **1-CN** and **2-CN** are new Strecker-type intermediates for the synthesis of α-amino acids, whereas new β-amino acid esters were prepared directly by two-carbon homologation.

Acknowledgment. We thank Ulrike Eggert and Lars Ole Haustedt for their help, Buchler GmbH Braunschweig for a gift of quincorine and quincoridine, and the Fonds der Chemischen Industrie for continued support of our work.

Supporting Information Available: X-ray data for **2-SPh** and spectroscopic data for each new compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Work up with KF/water increased the yield from 39 to 70%.

(16) Cambridge Crystallographic Data Centre CCDC 185368. The X-ray structure was plotted by Molekel 4.1. Flükiger, H. P.; Lüthi, H. P.; Portmann, S.; Weber, J. *Swiss Center for Scientific Computing*; Manno: Switzerland, 2000−2001.

(17) For a leading reference on iminium ions, see: Mayr, H.; Ofial, A. R.; Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013.

(18) *E* and *Z* isomers of [3.2.1]bicyclic imines with nitrogen in the nonbridgehead position: (a) Sheridan, R. S.; Ganzer, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6158. (b) Radziszewski, J. G.; Downing, J. W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799.