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A Novel, Stereoselective Silyl-Directed Stevens [1,2]-Shift of Ammonium Ylides

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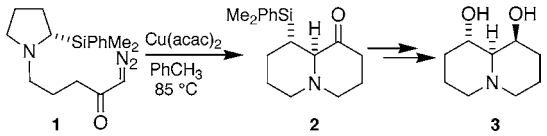
ABSTRACT



The silyl group of 2-silylpyrrolidines such as 1 plays several critical roles: a stereochemical control element in a facially selective carbenoid addition to the ring nitrogen, a stereochemical "placeholder" during regioselective 1,2-migration with retention by the resulting spirocyclic ammonium ylide, and a hydroxyl surrogate for an eventual stereoselective Fleming–Tamao oxidation. This chemistry represents a novel use of the Stevens rearrangement and offers a short, enantioselective route to hydroxylated quinolizidines such as 3 from Boc-pyrrolidine.

The Stevens rearrangement of ammonium ylides offers a convenient approach for the formation of new carbon−carbon bonds adjacent to nitrogen through a [1,2]-shift of one of the ammonium substituents to the neighboring ylide carbon.[1] Despite considerable mechanistic evidence in support of an intermediate radical pair, the Stevens [1,2]-shift has been shown to proceed with moderate to high retention of configuration when a chiral migrating group is employed.[2] A related issue concerns a chirality transfer from the stereogenic ammonium nitrogen to the adjacent carbon, which we have shown to be possible in the case of cyclic ammonium ylides.[3] A recently described synthesis of the alkaloid epilupinine in five steps from proline ester illustrated both of these points.[4] In this synthesis, the original proline stereocenter influences the configuration at the second, temporary one at nitrogen, which then permits the preservation of the original center during its [1,2]-shift, an example of the principle Seebach has labeled "self-regeneration of stereocenters".[5] One limitation of this methodology though is the need for a conjugating group on the migrating carbon, typically aryl or carbonyl,[6] presumably to stabilize the intermediate radical center.

The ease with which fused bicyclic amines of the quinolizidine, indolizidine, and pyrrolizidine classes might be constructed using spirocyclic ammonium ylide intermediates suggested the possible application of this approach to biologically important indolizidine or quinolizidine alkaloids,[7] as well as related unnatural analogues (Scheme 1). However, it was unclear how such polyhydroxylated skeletons could be efficiently assembled, given the apparent need for carbon-containing stabilizing groups in the key [1,2]-shift. For this reason, we set out to develop a new application of the Stevens rearrangement where a suitable hydroxyl surrogate ("X") could be used in place of a conjugating group and allow for smooth rearrangement followed by convenient conversion to the desired hydroxyl functionality. Here we describe a novel silyl-directed Stevens rearrangement and

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(1) (a) Sato, Y.; Shirai, N. *Yakugaku Zasshi* **1994**, *114*, 880−887. (b) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913−974. Lepley, A. R.; Guimanini, A. G. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 3, pp 297−440.

(2) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009−27.

(3) Glaeske, K. W.; Arif, A. M.; West, F. G. *Org. Lett*. **1999**, 31−33.

(4) (a) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565−16574. (b) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420.

(5) Review: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2709−2748.

(6) For a prior discussion of the scope of this chemistry, see: West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177−1178.

(7) Reviews: (a) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579−8629. (b) Elbein, A. D.; Molyneux, R. J. In *Iminosugars as Glycosidase Inhibitors*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999; pp 216−251. (c) Tyler, P. C.; Winchestter, B. G. In *Iminosugars as Glycosidase Inhibitors*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany 1999; pp 125−156. (d) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935−44.

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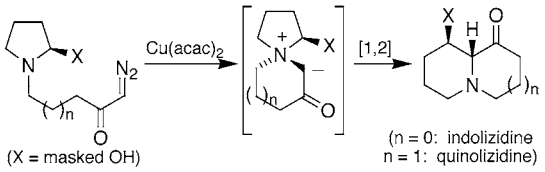
Scheme 1

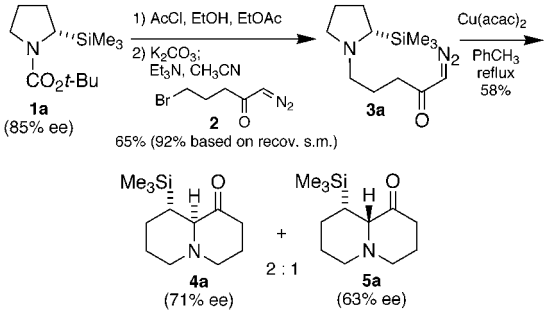


its application to the stereoselective construction of dihydroxyquinolizidines.

Combined with the ready accessibility of optically enriched 2-silylpyrrolidines using Beak's asymmetric lithiation methodology,[8] the proven utility of Fleming−Tamao-type oxidative desilylations[9] made the silyl group an obvious choice for exploring new methodology concerning the Stevens rearrangement. The success of this approach would depend on the ability of the silyl group to direct and/or facilitate the [1,2]-shift. A closer look at the literature revealed that in contrast to their ionic counterparts,[10] relatively little is known regarding the effect of silyl substitution on the generation or stability of adjacent radicals.[11] Wilt and co-workers reported an increased reactivity of α-halosilanes toward halogen abstraction by tin radicals but ascribed this to a kinetic polar effect rather than any special thermodynamic stability conferred by the silyl group.[12,13] Perhaps the closest recent experimental evidence in support of silyl α-carbon-centered radical stabilization is found in the report of Uemura and co-workers.[14] This work focused on the rhodium-catalyzed cycloaromatization of silylated acyclic enediynes followed by hydrogen abstraction with preferential formation of α-silyl vs *β*-silyl radicals. The uncertainty associated with the effect of silyl groups on adjacent radical centers provided an additional incentive for investigating the proposed silyl-directed [1,2]-shift chemistry.

An initial investigation of the feasibility of the silyl-directed [1,2]-shift strategy employed the known[8] (*S*)-*N*-Boc-2-trimethylsilylpyrrolidine **1a**, which was deprotected and alkylated with bromide **2**[6] (Scheme 2). Much to our delight, when diazoketone substrate **3a** was treated with 10 mol % $Cu(acac)_2$ in toluene at reflux,[4] it furnished quinolizidines **4a** and **5a** in 58% yield as a 2:1 ratio of separable diastereomers. The relative stereochemistry of the major

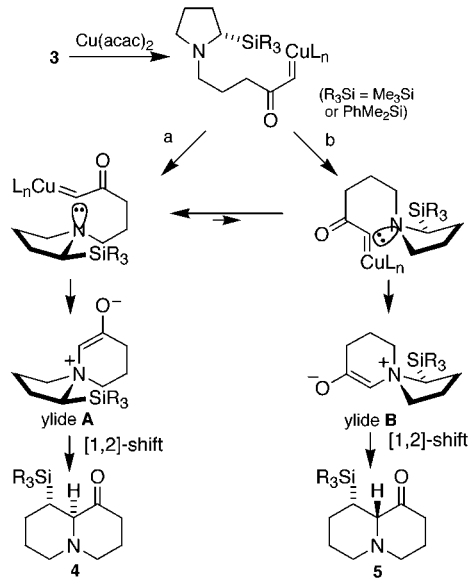
Scheme 2



isomer **4a**[15] is analogous to that seen in the related proline series from our labs.[4]

As in that example, stereoselectivity apparently results from the preferred attack of the intermediate metallocarbene cis to the larger non-hydrogen substituent at C-2, followed by migration with retention (Scheme 3). Assuming a pseu-

Scheme 3



doequatorial disposition of the large silyl group, we find that rapid pyramidal inversion at nitrogen permits two possible reactive forms leading to diastereomeric ylides **A** and **B**. Path a is expected to be favored due to a preference for the invertomer possessing a trans relationship between the silyl group and the carbene side-chain. This argument is consistent with results seen in our previous studies,[4] as well as those of Clark and co-workers.[16]

A homolysis/recombination mechanism can potentially furnish racemic products through a pathway in which the intermediate biradical suffers randomization. However, NMR

(8) (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am Chem. Soc.* **1994**, *116*, 3231−3239. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(9) (a) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7682. (b) Fleming, I. *Chemtracts: Org. Chem.* **1996**, 1−64.

(10) (a) Siehl, H.-U.; Muller, T. In *Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 1998; Vol. 2, Parts 1−3, pp 595−701. (b) Brinkman, E. A.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 8304−8310.

(11) Davidson, I. M. T.; Barton, T. J.; Hughes, K. J.; Ijadi-Maghsoodi, S.; Revis, A.; Paul, G. C. *Organometallics* **1987**, *6*, 4−646. For a recent report on the short lifetime of α-silyl radicals, see: Le Gall, E.; Hurvois, J.-P.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, *2645*, 5−2653.

(12) Wilt, J. W.; Belmonte, F. G.; Zieske, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 5665−5675.

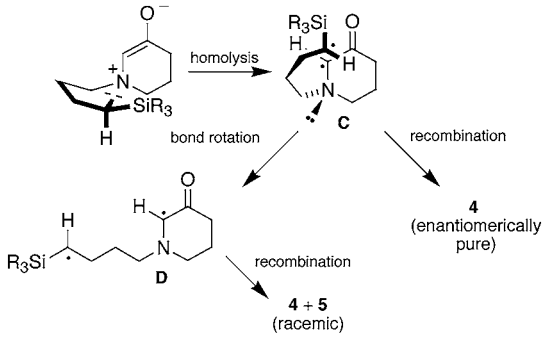
(13) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281−287.

(14) Manabe, T.; Yanagi, S.; Ohe, K.; Uemura, S. *Organometallics* **1998**, *17*, 2942−2944 and references therein.

(15) Strong support for this stereochemical assignment comes from the presence of a large 1,2-diaxial coupling between the adjacent bridgehead and silyl-substituted methines in the proton NMR spectrum.

analysis of **4a** and **5a** using the chiral shift reagent Eu(hfc)$_3$ showed that both were formed with significant stereochemical retention (84% for **4a** and 74% for **5a**).[17] This suggests that recombination of the initially formed biradical **C** is fast in comparison to bond-rotation to achiral biradical **D** (Scheme 4). To our knowledge, this represents the first

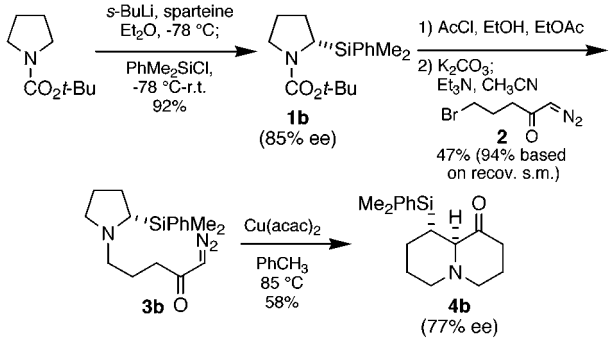
Scheme 4



example of a silyl-directed Stevens rearrangement. Though this novel [1,2]-shift is gratifying, this chemistry was not applicable to the synthesis of hydroxylated quinolizidines since the trimethylsilyl group is not suitable for subsequent Fleming−Tamao oxidation. At this point, we next turned our attention to the corresponding phenyldimethylsilyl derivative.

Asymmetric lithiation and silylation under the standard conditions[8] furnished (*S*)-*N*-Boc-2-phenyldimethylsilylpyrrolidine **1b** in 92% yield and 85% ee (Scheme 5).[18] The Boc

Scheme 5



group was removed with anhydrous HCl, and the free amine was alkylated as before with **2** to provide **3b** in 47% yield after 48% conversion.[19] Treatment of **3b** under the conditions used for the rearrangement of **3a** to **4a** + **5a** furnished quinolizidine **4b** as a single diastereomer in 55% yield.[20] A slight reduction in reaction temperature led to a small increase in yield, but at temperatures lower than 85 °C the reaction became sluggish. Other soluble copper catalysts also gave inferior results, as did $Rh_2(OAc)_4$.

It is interesting to note that **4b** was isolated as a single diastereomer, given the 2:1 ratio of **4a** to **5a** seen in the previous series. A possible explanation for this difference is a higher conformational rigidity of the pyrrolidine ring prior to carbenoid addition due to the increased steric bulk of the phenyldimethylsilyl group, leading to a greater preference for ylide diastereomer **A** (Scheme 3).

Quinolizidine **4b** was obtained in 77% ee (^{1}H NMR with Eu(hfc)$_3$), indicating 91% stereochemical retention[17] during the [1,2]-shift. This case displayed a higher degree of retention than either the trimethylsilyl example **3a** or the earlier proline-derived substrate.[4] It is possible that rate of randomization of the relatively more stable ester-substituted biradical in the proline example is faster than it is for the silyl-substituted biradicals. However, the improved degree of retention by **3b** over that by **3a**, although welcome, is not easily explained.

Finally, the suitability of the silyl-directing group as a hydroxyl surrogate needed to be investigated. Quinolizidine **4b** could be diastereoselectively reduced in high yield with Dibal-H[21] to furnish alcohol **6b** (Scheme 6).[22] Sodium borohydride furnished diastereomers **6b** and **7b** with a modest selectivity for axial attack product **7b**. Fleming−Tamao oxidation of **6b** under Denmark's conditions[23] proceeded smoothly to give quinolizidinediol **8b** in 91% yield.[24] Support for the stereochemical assignments of **6b** and **7b** was obtained by the conversion of the 1:4 mixture of **6b**/**7b** to **8b** and known symmetrical diol **9b**.[25]

(16) (a) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3325−3337. (b) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519−2522.

(17) Retention was calculated as % ee of quinolizidines **4a** (71%), **5a** (63%), or **5b** (77%) divided by % ee of **3a** or **3b** (both 85%).

(18) Optical purity of **1b** was determined by HPLC, using a Daicel CHIRACEL OD-H column with a mobile phase of 0.25% ^{i}PrOH/hex and a flow rate of 0.5 mL/min.

(19) Alkylation product **3b** was found to decompose slowly under the conditions of its formation, requiring that the reaction be stopped prior to complete consumption of starting material. The same problem, though less severe, was encountered in the alkylation of **3a**.

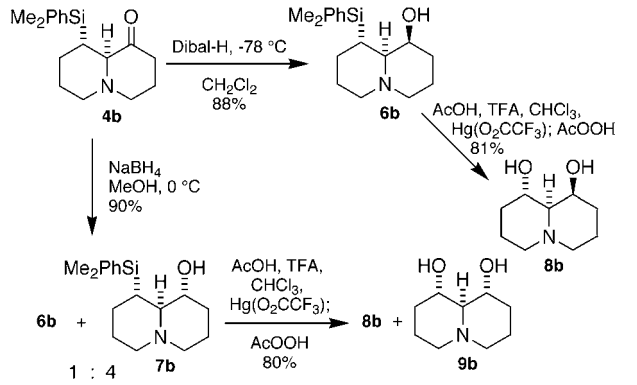
(20) **Representative Procedure for Conversion of 3b to 4b.** To a stirring solution of Cu(acac)$_2$ (0.011 g, 0.040 mmol) in a solution of degassed toluene (36 mL) at 85 °C was added a solution of diazoketone **3b** (0.123 g, 0.404 mmol) in degassed toluene (4.0 mL) via syringe pump over 1 h. Upon complete addition, the syringe was washed with 2 mL of toluene and the contents were added directly to the reaction. The resulting solution was allowed to cool to room temperature. The reaction mixture was concentrated and immediately loaded on a 1.5 × 10 cm column and eluted with a gradient of 20 mL each of 10, 20, and 40% EtOAc/hexanes collecting 2 mL fractions. Product-containing fractions were concentrated under reduced pressure to give **4b** (0.067 g, 58%) as a colorless oil. The product was a single isomer as determined by proton and carbon NMR: R_f 0.66 (10% MeOH/CH_2Cl_2); IR (neat) 2937, 2855, 2799, 2752, 1720 cm^{-1}; $[\alpha]^{20}_D$ +30.8 (*c* 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.32−7.31 (m, 3H), 2.95−2.85 (br m, 2H), 2.56 (d, J = 11.0 Hz, 1H), 2.40 (ddd, J = 11.0, 11.0, 4.0 Hz, 1H), 2.32 (ddd, J = 13.0, 3.5, 3.5 Hz, 1H), 2.16 (ddd, J = 13.5, 2.0, 2.0 Hz, 1H), 2.07 (ddd, J = 12.0, 12.0, 8.0 Hz, 1H), 1.97−1.88 (m, 2H), 1.75−1.70 (br m, 1H), 1.59−1.44 (m, 2H), 1.39 (ddd, J = 14.5, 11.0, 3.5 Hz, 1H), 1.14 (dddd, J = 13.5, 12.8, 12.8, 4.0 Hz, 1H), 0.32 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 139.2, 134.4, 128.8, 127.6, 72.7, 56.4, 55.4, 40.3, 26.8, 26.2, 26.2, 22.6, −2.1, −2.7. Anal. Calcd for $C_{17}H_{25}NOSi$: C, 71.03; H, 8.77; N, 4.87. Found: C, 71.0; H, 8.93; N, 4.52.

(21) Reduction with L-selectride or under Meerwein−Pondorff−Verley conditions also gave **6b** exclusively, but in slightly lower yield.

(22) 2D NOESY NMR data clearly indicated the expected axial alcohol resulting from equatorial attack of the bulky hydride reagent.

(23) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875−2886.

Scheme 6



Polyhydroxylated quinolizidines have been identified in recent years as potential glycosidase inhibitors[26] in analogy to the better known indolizidines. The strategy described above offers a short and flexible route to such compounds.

This work constitutes the first examples of silyl-directed Stevens [1,2]-shifts of ammonium ylides. Migration occurs with high retention in the case of **3b**, offering a unique application of Beak's asymmetric lithiation methodology. Subsequent stereoselective ketone reduction and Fleming−Tamao oxidation affords the corresponding diols. This route furnishes dihydroxyquinolizidines in six steps from readily available Boc-pyrrolidine. Additional examples of this chemistry involving other ring skeletons will be described elsewhere.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Approximate ee of diol **8b** was found to be 60% ee (NMR chiral shift analysis with Eu(hfc)$_3$), indicating a small degradation in optical purity of **4b** during the subsequent manipulations.

(25) Marquart, A. L.; Podlogar, B. L.; Huber, E. W.; Demeter, D. A.; Peet, N. P.; Weintraub, H. J. R.; Angelastro, M. R. *J. Org. Chem.* **1994**, *59*, 2092−2100.

(26) (a) Schaller, C.; Vogel, P. *Helv. Chim. Acta* **2000**, *83*, 193−232. (b) Overkleeft, H. S.; Bruggeman, P.; Pandit, U. K. *Tetrahedron Lett.* **1998**, *39*, 3896−3872. (c) Carretero, J. C.; Arrrayas, R. G.; De Garcia, I. S. *Tetrahedron Lett.* **1997**, *38*, 8537−8540. (d) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5537−5545.