A Novel Aryl Migration from Silicon to Carbon: An Efficient Approach to Asymmetric Synthesis of α-Aryl β-Hydroxy Cyclic Amines and Silanols

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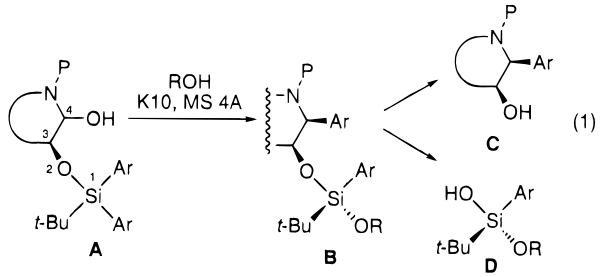
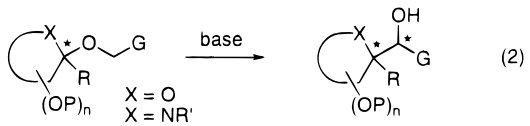
Currently much attention has been focused on stereochemically defined α-substituted cyclic amines because of their diverse physiological activities[1] and hence several stereoselective methods for their syntheses have been developed, including organometallic additions to cyclic *N*-acyliminium ions,[2] electrophilic substitutions of α-metallo cyclic amines,[3] and cyclizations of α-substituted acyclic amines.[4] Herein we wish to report a new, efficient entry to α-aryl β-hydroxy cyclic amines **C** via the novel 1,4-aryl migration from silicon to carbon which was discovered by chance in the reaction of β-*tert*-butyldiarylsiloxy cyclic hemiaminal **A** with an alcohol promoted by montmorillonite K10 clay (eq 1). The



(1)

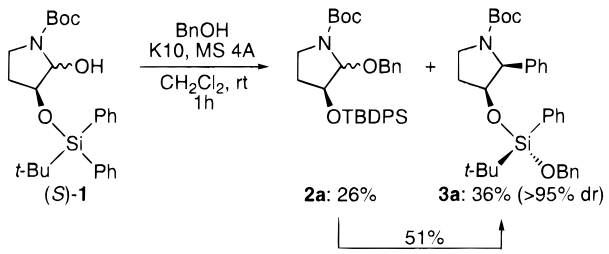
most striking feature of the aryl migration process is that the displacement at the silicon proceeds in a highly diastereoselective fashion to create the single configuration at the Si-centered chiral center, thereby permitting ready access to enantio-enriched alkoxysilanols **D**.

The details of the discovery of the novel aryl migration are as follows. Recently, we have developed the acetal [1,2]-Wittig rearrangement protocol by which *O*-glycosides (cyclic acetals) can be converted to the *C*-glycosides with high diastereoselectivity (eq 2, X = O).[5] Thus, we envisioned that application of the [1,2]-



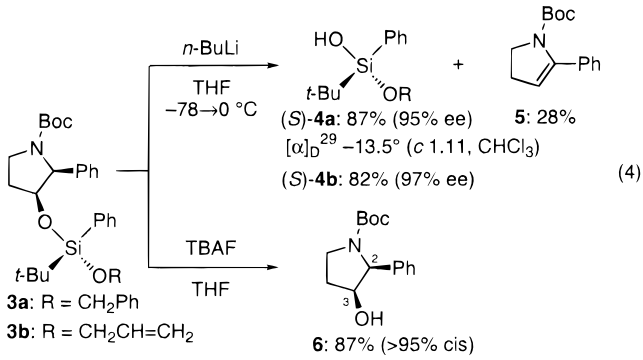
(2)

Wittig protocol to aminals (cyclic *N*,*O*-acetal) could provide the α-substituted cyclic amines of synthetic interest (X = NR′). To this end, we first attempted the preparation of the requisite aminal **2a** from the β-*tert*-butyldiphenylsiloxy cyclic hemiaminal (*S*)-**1** (98% ee)[6] and benzyl alcohol using montmorillonite K10 clay



(3)

(K10) and molecular sieves 4A (MS 4A) which has worked well for the preparation of *O*-glycoside from the hemiacetals.[7,8] To our surprise, the reaction was found to yield the unexpected phenyl migration product **3a**[9] in moderate yield as the almost single diastereomer, along with a small amount of the expected benzyl aminal **2a** (eq 3).[10] Aminal **2a** thus obtained was also converted to α-phenylpyrrolidine **3a** under similar reaction conditions. This result indicates that one of the phenyl groups in TBDPS migrates from the silicon to the α-amino carbon in a cis fashion, and at the same time benzyl alcohol attacks the silicon in a highly diastereoselective manner to create the single configuration at both the α-amino carbon and the silicon center. Indeed, treatment of **3a** with *n*-BuLi (3 equiv) in THF at −78 to 0 °C was found to liberate the chiral benzyloxysilanol (*S*)-**4a** with extremely high enantiomeric excess (95% ee) in 87% yield,[11] together with the formation of the α-phenyldihydropyrrole **5** (eq 4). On the other hand,



(4)

desilylation of **3a** by tetrabutylammonium fluoride (TBAF) gave the *cis*-α-phenyl-β-hydroxypyrrolidine **6** (>95% dr) in good yield. A similar reaction of **1** with allyl alcohol gave the *Si*-allyloxy phenyl migration product **3b** (62%), in comparably high stereoselectivities, and **3b** was also converted to the chiral allyloxysilanol (*S*)-**4b** (82%, 97% ee)[11] or pyrrolidine **6** (87%, >95% cis).

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(1) *The Alkaloids, Chemistry and Biology*; Cordell, G. A., Ed.; Academic: San Diego, 1998; Vol. 50.

(2) For a recent example, see: Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075−5076 and references therein.

(3) (a) Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471−523. (b) Meyers, A. I. *Aldrichim. Acta* **1985**, *18*, 59−68.

(4) (a) Bringmann, G.; Ewers, C. J.; Walter, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 733−762. (b) Nadin, A. *Contemp. Org. Synth.* **1997**, 387−414. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633−640.

(5) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317−3318.

(6) This compound was derived from (*S*)-3-hydroxypyrrolidin-2-one in three steps: (i) TBDPSCl, imidazole; (ii) $(Boc)_2O$, Et_3N; (iii) $NaBH_4$/MeOH. (*S*)-3-Hydroxypyrrolidin-2-one was prepared according to the literature procedure: Sarairi, D.; Maurey, G. *Bull. Soc. Chim. Fr.* **1987**, 297−301. The details are described in the Supporting Information.

(7) (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520−522. (b) Tomooka, K.; Nakamura, Y.; Nakai, T. *Synlett* **1995**, 321−322.

(8) The general procedure is as follows: Cyclic hemiaminal **1** (369 mg, 0.835 mmol) and benzyl alcohol (0.173 mL, 1.67 mmol) in CH_2Cl_2 (11 mL) was added to flame-dried MS 4A (2.0 g) in a two-necked flask. The resulting mixture was stirred at room temperature for 0.5 h. Flame-dried montmorillonite K10 (1.5 g) was added to the suspension and stirred vigorously at that temperature for 1 h. Then the resulting mixture was filtrated through a pad of Celite. Evaporation of the filtrate gave the crude product. Purification by silica gel chromatography gave 116 mg (26%) of benzyl aminal **2a** and 165 mg (36%) of α-phenylpyrrolidine **3a**. The diastereomeric ratio of these compounds was determined by ^1H NMR analysis.

(9) The structure of **3a** was determined by X-ray crystallography, see the Supporting Information.

(10) The product ratio depended upon the reaction time: aminal **2a** (26% for 1 h, and 13% for 12 h) and α-phenylpyrrolidine **3a** (36% for 1 h and 46% for 12 h). Obviously, aminal **2a** initially formed is gradually converted to **3a** under the reaction conditions.

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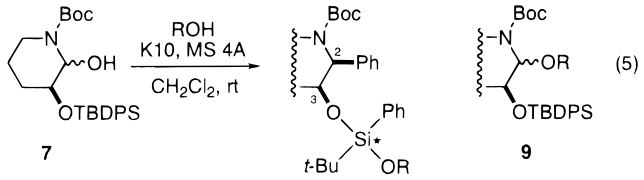
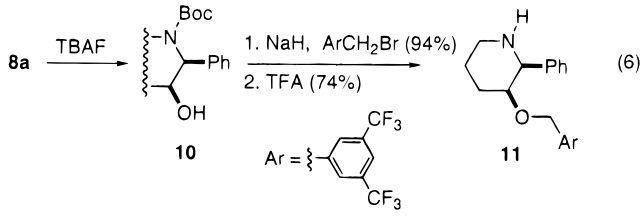
Next, we examined the reaction of piperidine hemiaminal **7** (*racemic*) with various alcohols in a similar way (eq 5). These

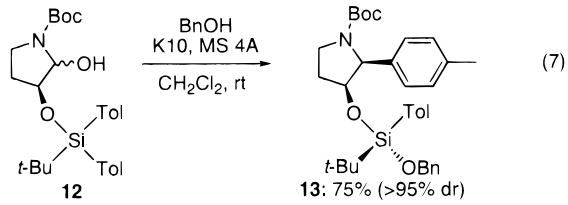


reactions resulted in the exclusive formation of the corresponding phenyl migration product **8a**−**d** in a highly diastereoselective fashion to provide >95% cis at the α-carbon and >80% dr at the silicon center; none of aminal **9** was formed.[12] Treatment of **8a** (R = benzyl) with TBAF gave *cis*-α-phenyl-*β*-hydroxypiperidine **10** which was then converted to the known antagonist **11** of the neurokinine substance P (eq 6).[13] This is one example to



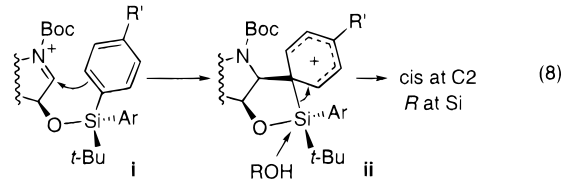
demonstrate the synthetic potential of the present novel reaction as a method for the synthesis of α-aryl *β*-hydroxy cyclic amines, a class of compounds of biological importance.

Further experimentation was undertaken to elucidate the mechanism of this novel phenyl migration process. First, the unique character of the K10/MS 4A system was evaluated in the reaction of **7** with benzyl alcohol. While the absence of MS 4A led to the formation of a mixture of **8a** and its *Si*-hydroxy analogue **8e** (R = H), the use of PPTS (0.1 equiv), *p*-TsOH (0.1 equiv), and $BF_3 \cdot OEt_2$ (2.0 equiv) all resulted in the exclusive formation of benzyl aminal **9** (R = Bn) in 90−98% yields; none of **8a** was formed. Thus, these observations reveal that the present phenyl migration can effectively occur only under the unique action of K10/MS 4A. Second, a similar K10-promoted reaction of benzyl aminal **9** with allyl alcohol (1.0 equiv) was found to result in the formation of a mixture of **8b** (R = allyl) and **8a** (R = benzyl) in 70:30 ratio. Furthermore, when the K10-promoted reaction of benzyl aminal **9** was carried out *in the absence of any alcohol*, only a trace of **8a** was formed. These results suggest that addition of an alcohol substantially facilitates the phenyl migration process. Third, a similar reaction of *tert*-butylbis(*p*-tolyl)silyloxy analogue



12[14] gave *p*-tolyl substituted pyrrolidine **13** as the sole product, indicating that the aryl migration occurrs at the ipso position (eq 7).

A plausible mechanism of this 1,4-migration is shown in eq 8. The mechanism most likely involves the *N*-acyliminium ion **i** which should be in equilibrium with either the hemiaminal or the aminal once formed from **i** and the alcohol added. Then, species **i** undergoes an intramolecular Friedel−Crafts reaction[15] onto one of the aryl groups on the silicon in a highly diastereoselective manner to form the *β*-silyl cation **ii** which is then collapsed by alcohol attack onto the silicon to give the 1,4-phenyl migration product.[16,17]



In summary, we have described a novel 1,4-aryl migration that occurs on *β*-*tert*-butyldiarylsiloxy pyrrolidine and piperidine hemiaminals under the action of K10/MS 4A in a highly stereoselective manner. This new reaction provides a novel, efficient entry to α-aryl *β*-hydroxy cyclic amines of synthetic value as well as enantio-enriched alkoxysilanols which are otherwise difficult to obtain.[18] Further work is in progress to elucidate the mechanism of this process and enhance the synthetic potential thereof.

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Supporting Information Available: Experimental procedures with spectroscopic data for compounds **1**−**13** and crystallographic data of **3a** and **8e** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The absolute configuration of (*S*)-**4a** was assigned from the stereochemistry of **3a**, based on the reasonable postulate that the *β*-elimination proceeds without loss of the configurational integrity at the silicon. The enantiomeric excess of **4a** and **4b** was determined by HPLC analysis using a Daicel CHIRACEL OD column with hexane/2-propanol as a solvent.

(12) The diastereomeric ratios at the silicon were determined by ^{1}H NMR analysis. The cis stereochemistry of **8a** was established by X-ray analysis after conversion (H_2/Pd−C) to **8e** (eq 5, R = H).

(13) (a) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545−2550. (b) Lowe, J. A., III; McLean, S. *Curr. Pharm. Des.* **1995**, *1*, 269−278.

(14) This compound was prepared from (*S*)-hydroxypyrrolidin-2-one in a manner similar to **1**. The corresponding silyl ether was derived from *tert*-butylbis(4-methylphenyl)silanol and (*S*)-hydroxypyrrolidin-2-one in the presence of oxalyl chloride according to the literature procedure: Tanino, K.; Yoshitani, N.; Moriyama, F.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 4206−4207. Lennon, P. J.; Mack, D. P.; Thompson, Q. E. *Organometallics* **1989**, *8*, 1121−1122.

(15) Related example of intramoleculer Friedel−Crafts reaction, see: Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698−8700.

(16) Related examples of phenyl migration reaction from silicon to carbon have been reported. For 1,4- or 1,5-phenyl or vinyl migration promoted by Lewis acids, see: (a) Archibald, S. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2387−2390. (b) Hioki, H.; Izawa, T.; Yoshizuka, M.; Kunitake, R.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2289−2992. For 1,2-phenyl migration promoted by fluoride ion, see: (c) Morihata, K.; Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *36*, 5555−5558.

(17) Obviously, more detailed studies are needed to elucidate the exact mechanism, particularly concerning the specific role of K10 and the steric course of the substitution on the silicon. Semiempirical calculations on the transition states are underway.

(18) A few synthetic methods for enantio-enriched silanol have been reported. For resolution or separation of racemic or diastereomeric silanols, see: (a) Tacke, R.; Linoh, H.; Ernst, L.; Moser, U.; Mutschler, E.; Sarge, S.; Cammenga, H. K.; Lambrecht, G. *Chem. Ber.* **1987**, *120*, 1229−1237. (b) Yamamoto, K.; Kawanami, Y.; Miyazawa, M. *J. Chem. Soc., Chem. Commun.* **1993**, 436−437. (c) Feibush, B.; Woolley, C. L.; Mani, V. *Anal. Chem.* **1993**, *65*, 1130−1133. (d) Mori, A.; Toriyama, F.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1999**, 549−550. For stereospecific oxidation of enantio-enriched silanes or halosilanes, see: (e) Cavicchioli, M.; Montanari, V.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 6329−6330. (f) Adam, W.; Mitchell, C. M.; Saha-Möller, C. R.; Weichold, O. *J. Am. Chem. Soc.* **1999**, *121*, 2097−2103 and references therein.