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Chirality Transfer from Carbon to Nitrogen to Carbon via Cyclic Ammonium Ylides

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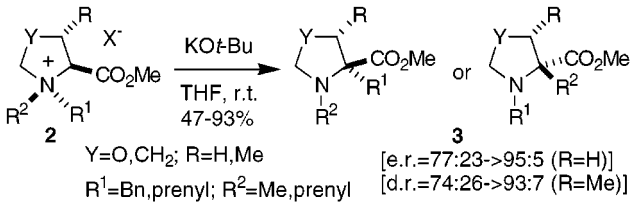
ABSTRACT



Cyclic ammonium salts 2 were prepared by diastereoselective quaternization of nitrogen in the corresponding proline or threonine derivatives. Upon treatment with base, salts 2 underwent [1,2]- or [2,3]-shift to 3 with moderate to complete stereospecificity. The overall process entails chirality transfer from the original α carbon to the neighboring nitrogen and then back to the carbon.

Chirality transfer from carbon to carbon via sigmatropic rearrangements is a well-established approach in asymmetric synthesis.[1] However, transfer of stereochemical information from a chiral *heteroatom* to carbon is much less common. While sulfur ylides have enjoyed considerable attention in this area,[2] several examples involving base-induced rearrangements of chiral quaternary ammonium salts also have been reported.[3] Our observation of high levels of stereoselectivity in the rearrangement of a metallocarbene-derived spirocyclic ammonium ylide,[4] along with those of Clark[5] and McMills,[6] prompted our interest in exploring N → C chirality transfer under more controlled conditions. In particular, we were interested in forming a quaternary ammonium salt of known configuration before generating the short-lived ylide. Here we describe preliminary results of chirality transfer by [1,2]- or [2,3]-shift of several cyclic ammonium ylides stereogenic at nitrogen.

We chose to limit our initial focus to cyclic ylides with exocyclic migrating groups, since these cases seemed most likely to preserve the stereochemical information during migration from N to C. We envisaged fast recombination of

(1) (a) Hill, R. K. In *Comrehensive Organic Synthesis*; Trost, B. M., Fleming, Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 7.1. (b) Brückner, R. In *Comrehensive Organic Synthesis*; Trost, B. M., Fleming, Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 4.6.

(2) (a) Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962. (b) Kurth, M. J.; Hasan, T. S.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286. (c) Cagle, P. C.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 3655.

(3) (a) Hill, R. K.; Chan, T.-H. *J. Am. Chem. Soc.* **1966**, *88*, 866. (b) Brewster, J. H.; Jones, R. S., Jr. *J. Org. Chem.* **1969**, *34*, 354. (c) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, 1077. (d) Stará, I. G.; Star'y, I.; Tich'y, M.; Závada, J.; Hanus, V. *J. Am. Chem. Soc.* **1994**, *116*, 5084. For an especially relevant study involving stereoselective [2,3]-shifts of configurationally stable *N*-allyl-2-lithiopyrrolidines and -pyrrolidinium salts, see: (e) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817.

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

(5) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519.

(6) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165.

(7) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442.

(8) General Procedure for Salt Formation: Preparation of **2a**. MeI (3.73 mL, 60 mmol) was added neat to **1a** (6.57 g, 30 mmol), and the mixture was stirred for 1 h. Excess MeI was removed under reduced pressure, and the brown residue (4:1 crude mixture of diastereomers) was dissolved in CH_2Cl_2 (150 mL) and layered with Et_2O (200 mL). Three recrystallizations (CH_2Cl_2/Et_2O) provided 8.37 g (77%) of **2a** as white needles: mp 140−141 °C; $[\alpha]^{22}_D = -41.9°$ ($c = 0.25$, CH_2Cl_2); IR (KBr) 2976, 1757, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63−7.59 (m, 2H), 7.54−7.44 (m, 3H), 5.46 (dd, 1H, $J = 9.0$, 9.0 Hz), 5.35 (d, 1H, JAB = 12.9 Hz), 5.09 (d, 1H, JAB = 12.9 Hz), 4.54 (app. q, 1H, $J = 10.8$ Hz), 3.85 (s, 3H), 3.43 (ddd, 1H, $J = 10.5$, 8.1, 1.8 Hz), 3.16 (s, 3H), 2.83−2.70 (m, 1H), 2.50−2.12 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 133.7, 131.5, 130.0, 128.9, 72.1, 66.8, 64.9, 54.3, 45.3, 25.0, 19.1. Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.64; H, 5.59; N, 3.85.

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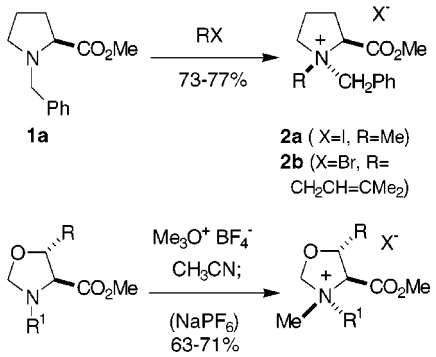
the radical pair intermediates in the [1,2]-shift before the migrating radical could diffuse to the opposite face of the heterocyclic ring and assumed exclusive delivery of the allyl unit to the same face during a concerted [2,3]-shift. *N*-Benzylproline methyl ester **1a**[7] could be alkylated stereoselectively with methyl iodide or prenyl bromide and fractionally crystallized to give salts **2a**,**b** (Scheme 1).[8] The

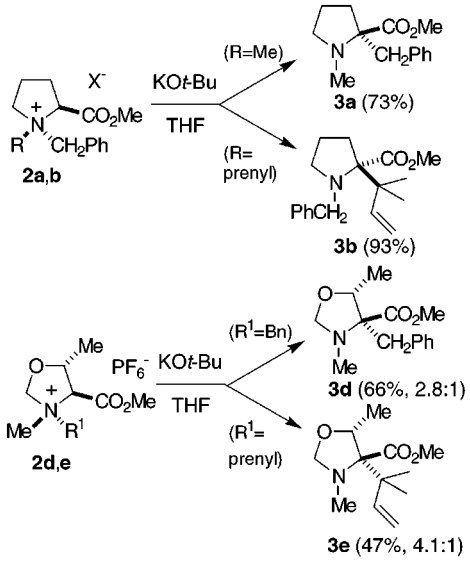
Scheme 1



expected approach of alkyl halide from the same face as the ester group[9] (due to a preferred N pyramidal form in which the benzyl and carbomethoxy groups are trans disposed) was confirmed in the case of **2b** by X-ray crystallographic analysis.[10] Serine- and threonine-derived oxazolidines **1b**−**d**[11] could also be quaternized to give **2c**−**e**, though the diminished nucleophilicity of the nitrogen necessitated the use of the more reactive Me_3OBF_4. In the case of **2e**, it was not possible to isolate the major salt in pure form, so it was carried on as a 4.4:1 mixture of diastereomers.

After an extensive survey of reaction conditions, it was found that potassium *tert*-butoxide in THF was optimal for effecting the desired ylide formation/rearrangement process (Scheme 2). Thus, proline derivatives **2a**,**b** furnished [1,2]-

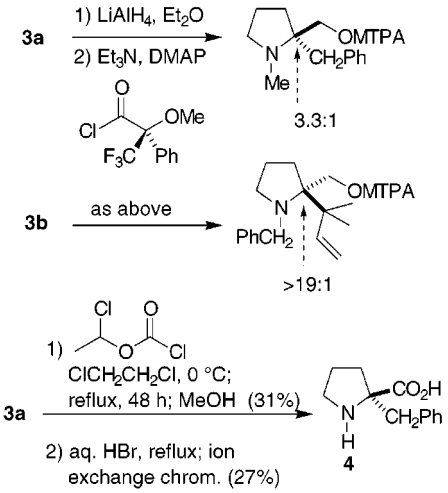
Scheme 2



and [2,3]-shift products **3a**,**b** in 73% and 93% yields, respectively.[12] In the case of oxazolidinium salts **2c**−**e**, we were concerned about possible fragmentative opening of the ylide. Serine derivative **2c** did suffer rapid destruction with no apparent [1,2]-shift, though we were unable to determine the fate of this material. On the other hand, threonine derivatives **2d**,**e** underwent conversion to products **3d**,**e** in moderate to good yield and as 2.8:1 and 4.1:1 mixtures of diastereomers, respectively (determined by ^{1}H NMR integration of methyl ester singlets).

The second stereocenter in oxazolidines **3d**,**e** functioned as a reporter group to allow facile measurement of product ratios. Proline derivatives **3a**,**b** were reduced to the corresponding prolinols and derivatized as (*R*)-MTPA esters (Scheme 3). ^{19}F NMR analysis indicated a 3.3:1 ratio of diastereomers for **3a** and a single diastereomer for **3b**. To confirm an (*R*)-configuration for the major enantiomer, **3a**

Scheme 3



(9) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831.

(10) Glaeske, K. W.; Arif, A. M.; West, F. G. Manuscript in preparation.

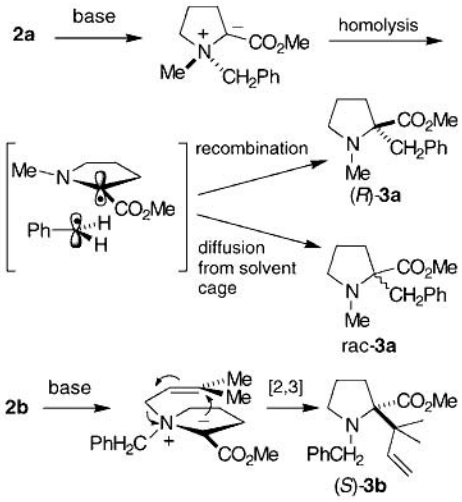
(11) **1b**−**d** were prepared by condensation of formaldehyde with the corresponding *N*-benzyl or *N*-prenyl methyl esters of serine or threonine.[10]

(12) General Procedure for Ylide Rearrangement: Preparation of **3a**. Solid KO-*t*-Bu (112 mg, 1.0 mmol) was added to a solution of **2a** (361 mg, 1.0 mmol) in THF (10 mL), and the reaction was stirred at room temperature for 1.5 h; then the solution was filtered through a Celite plug and concentrated to give a yellow residue. Purification by column chromatography (silica gel, 2.5-cm × 15-cm column, 1:1 Et_2O/hexanes) gave 171 mg (73%) of **3a** as a pale yellow oil: R_f 0.31 (1:1 Et_2O/hexanes); IR (neat) 2951, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.17 (m, 5H), 3.60 (s, 3H), 3.29 (d, 1H, J_{AB} = 13.5 Hz), 2.99 (dt, 1H, J = 8.7, 3.0 Hz), 2.71 (d, 1H, J_{AB} = 13.5 Hz), 2.60 (dd, 1H, J = 16.2, 7.8 Hz), 2.42 (s, 3H), 2.02 (ddd, 1H, J = 13.8, 10.8, 9.0 Hz), 1.83−1.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 137.6, 130.3, 127.8, 126.1, 71.1, 54.4, 50.9, 40.1, 35.5, 33.4, 21.5. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.83; H, 8.24; N, 6.04.

was correlated with the known (−)-2-benzylproline[13] **4** by demethylation with chloroethyl chloroformate[14] and saponification, furnishing material with an optical rotation of −11.3° (lit. −19.25°, 59% ee). Stereochemistry was assigned by analogy in the other examples.

In all cases, the configuration at the quaternary nitrogen center of **2** was established through cis-selective alkylation controlled by the adjacent stereocenter at C-2. As noted above, it was our expectation that the disposition of the migrating group would favor its delivery to that face of the planar ylide carbon after deprotonation. For examples involving a [1,2]-benzyl shift (**2a**,**c**), ratios of ca. 3:1 were obtained, suggesting that the rate of radical pair recombination from the same face is competitive with that of diffusion to the opposite face or out of the solvent cage entirely (Scheme 4). Ollis' studies indicate that this selectivity might be amplified by use of a more viscous solvent;[15] unfortunately, yields of **3** were disappointingly low when ylide formation was attempted in other solvent systems. Exclusive migration of the prenyl group was observed for substrate **2b**, and only in the [2,3] mode.[16] Moreover, product **3b** was obtained as a single enantiomer, consistent with the notion that a [2,3]-shift would be restricted to the same face. Substrate **2e** gave qualitatively similar results, though the situation was complicated by the need to carry out the rearrangement on a mixture of diastereomers and the uncertainties associated with a lower yield.

Scheme 4



The methodology described here provides a stereoselective route to α-quaternary amino acid derivatives through a novel chirality transfer approach. Formation of a temporary chiral center at nitrogen permits the facially selective migration of one of the N-substituents via ammonium ylide intermediates. Further studies of this stepwise approach, as well as complementary carbenoid-based methods, will be reported elsewhere.

Acknowledgment. We thank the American Cancer Society, the Petroleum Research Fund, and the University of Utah for financial support.

Supporting Information Available: Physical data for **2b**−**e** and **3b**,**d**,**e** and procedures for determining stereochemical ratios for **3a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(14) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.

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

(16) Competing [1,2]-shift has been observed in some cases for allyl-substituted ammonium ylides: (a) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051. (b) Beall, L. S.; Padwa, A. *Tetrahedron Lett* **1998**. *39*, 4159. See also ref 6.