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Stereochemical Course of [2,3] Anionic and Ylide Rearrangements of Unstabilized α-Aminoorganolithiums

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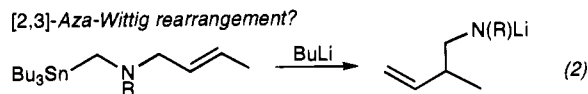Coral Gables, Florida 33124-0431*

The [2,3]-sigmatropic (Wittig) rearrangement of allylic ethers has been the subject of considerable interest over the past 50 years, and synthetic applications have increased since Still showed[1] that the rearrangement may be initiated by tin−lithium exchange of an α-alkoxy stannane (eq 1).[2] This observation was important for the synthesis of enantiopure compounds because of the configurational stability of the intermediate α-alkoxyorganolithiums. Recently, three independent studies showed that the reaction is stereospecific and proceeds with inversion of configuration at the lithium-bearing carbon.[3]

[2,3]-*Still-Wittig rearrangement*
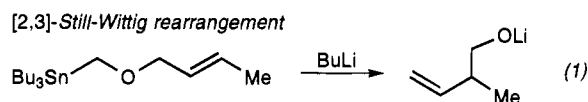
The analogous reaction involving α-aminoorganostannanes (eq 2) is rare, especially among unstabilized carbanions. Usually, the "carbanionic carbon" is stabilized by a double bond, an aromatic ring, or a carbonyl, and when they occur, [2,3]-rearrangements are driven by relief of ring strain.[4] One example of an aza-Wittig rearrangement of an unstabilized α-aminoorganolithium, induced by reductive lithiation of an *S,N*-acetal, was reported by Broka in 1989.[5] In 1993, Coldham reported two examples of aza-[1,2]-Wittig rearrangements initiated by tin−lithium exchange, which proceed by a radical mechanism.[6] In both cases, the α-aminoorganolithium is acyclic. We are not aware of any previous examples of aza-[2,3]-Wittig rearrangements of unstabilized α-aminoorganolithiums (eq 2), but we now report that this mechanism can compete with a [1,2]-pathway for 2-lithio-*N*-allylpyrrolidine. We also find that the aza-[2,3]-Wittig rearrangement proceeds with inversion of configuration at the lithium-bearing carbon, in accord with precedent in the oxygen series.[3]

[2,3]-*Aza-Wittig rearrangement?*

When the nitrogen is quaternary, the corresponding organo-

lithium is an ylide, and the [2,3]-rearrangement of *N*-allyl nitrogen ylides (eq 3) is more facile.[7] We also report three examples of this reaction, including one that establishes the stereospecificity of the reaction.

[2,3]-*Ylid rearrangement*

Recently, we showed that 2-lithio-*N*-methylpyrrolidines and 2-lithio-*N*-methylpiperidines possess remarkable configurational stability[8] and that they undergo highly selective reactions with a variety of electrophiles, including aldehydes, ketones, and alkyl halides (eq 4).[9] With most carbonyl electrophiles, the configuration of the metal-bearing carbon is retained, while with primary alkyl halides inversion is observed. In the case of 2-lithiopiperidines, inversion is complete (≥99%), whereas with pyrrolidines, approximately 21−22% retention is observed.[9] Because of the extraordinary stability and unique reactivity of these lithiated heterocycles, we decided to investigate the reactivity of these compounds toward sigmatropic rearrangements.
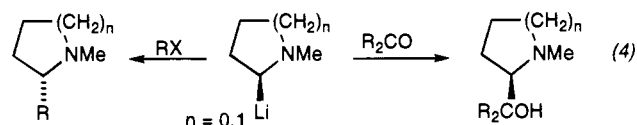
(S)-N-BOC-2-(tributylstannyl)pyrrolidine was prepared in 94% ee by asymmetric deprotonation and stannylation according to the method of Beak,[10] as shown in Scheme 1. Removal of the BOC group with bromocatechol borane[11] and alkylation with allyl bromide afforded (*S*)-**1a** in 51% yield. The transmetalation of **1a** with butyllithium was complete in 15−20 min at −78 °C, as indicated by TLC, a reactivity that is similar to that of its *N*-methyl analog.[8,9] Considering that Still−Wittig rearrangements typically occur at temperatures below −50 °C, we were somewhat surprised to discover that organolithium **2a** did not rearrange until warmed to >10 °C. Optimum conditions for the rearrangement were found to be 13 °C in THF/TMEDA. At lower temperatures, no rearrangement occurred. At room temperature, or in the absence of TMEDA, significantly more racemization occurred. To avoid loss of product due to anticipated volatility, and to aid in analysis of enantiomeric purity, the reaction mixture was cooled to −78 °C and quenched with α-naphthoyl chloride. After workup, naphthamide **3a** was obtained in 64% yield. Pirkle analysis[12] revealed the major isomer to be *S*, with an enantiomeric purity of 48% ee. The absolute configuration of **3a** was assigned by the order of elution on the Pirkle column and was confirmed by independent synthesis.[13] The enantiomer ratio obtained indicates that this aza-Wittig rearrangement occurs with approximately 76%

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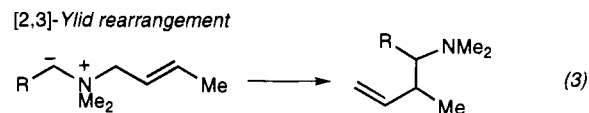
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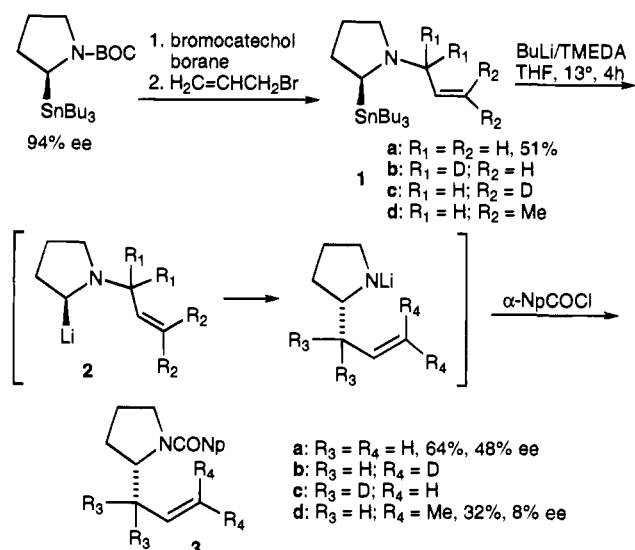
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Communications to the Editor

Scheme 1

a: $R_1 = R_2 = H$, 51%
b: $R_1 = D$; $R_2 = H$
c: $R_1 = H$; $R_2 = D$
d: $R_1 = H$; $R_2 = Me$

a: $R_3 = R_4 = H$, 64%, 48% ee
b: $R_3 = H$; $R_4 = D$
c: $R_3 = D$; $R_4 = H$
d: $R_3 = H$; $R_4 = Me$, 32%, 8% ee

Scheme 2

4a, 70%
4b, 75%

6a: R = H, 67%, 88% ee
6b: R = Me, 71%, 94% ee

Scheme 3

94%ee

7 (94% ee)

inversion and 24% retention of configuration at the lithium-bearing carbon.[14] This lack of stereospecificity is partly due to racemization of the organolithium, as shown by quenching the reaction with tributyltin chloride after 2 h and recovering 1a in 65% ee. It is also partly due to competitive [1,2]- and [2,3]-rearrangement pathways,[15] as shown by an experiment with regioselectively deuterated educt. Specifically, when a 7:1 ratio of 1b and 1c was subjected to the rearrangement, 3b and 3c were obtained in a ratio of 4.3:1. Assuming that [1,2]- and [2,3]-rearrangements are the only operative mechanisms, and that the [1,2]-(radical) mechanism scrambles the label (*i.e.*, 3b/3c = 1) while the [2,3]-mechanism does not, this corresponds to 53% of the rearrangement proceeding by a [2,3]-mechanism and 47% by a [1,2]-pathway.[16] Steric influences are important in the rearrangement, as shown by the reaction of 1d, which afforded racemic 3d in low yield, indicating exclusive [1,2]-rearrangement in this case.

Considering that *N*-methyl-2-lithiopyrrolidine racemizes at temperatures above −40 °C, the 74:26 enantiomer ratio is actually quite surprising. TLC monitoring of the reaction was done, however, and 13 °C for 4 h was indeed necessary for optimum yield! The fact that 1 is recovered in 65% ee after 2 h at 13 °C suggests that 2 possesses remarkable configurational and chemical stability. Additionally, the degree of racemization of 2 at 50% conversion suggests that a lower enantiomer ratio of 3 should have been obtained at 100% conversion, given the 53:47 [2,3]/[1,2]-mechanism ratio. A complete explanation of this anomaly is not possible at this time, but two possibilities come to mind. The first is experimental error in the integration of peaks in the chromatogram and the NMR spectrum. The second is that there may be aggregation of 2. In the latter instance, it may be that heterochiral aggregates (which would accumulate as 2 racemizes) are less reactive than either the monomer or a homochiral aggregate.[17] Coldham also observed anomalies that were attributed to aggregation in his study of the aza-Wittig rearrangement.[6]

As shown in Scheme 2, the transmetalation of *N,N*-diallyl-2-(tributylstannyl)pyrrolidinium ions and the ensuing [2,3]-

rearrangement is extremely facile. Removal of the BOC group as before and alkylation with excess allyl bromides afforded quaternary salts 4, which were purified by recrystallization. Transmetalation was again facile, but this time the rearrangement was immediate. That the rearrangement was a [2,3]-rearrangement (as shown) and not a [1,2]-rearrangement was demonstrated by obtention of 6b from 4b. The crude NMR spectrum showed only two *gem*-dimethyl groups, one that was allylic and one that was not, ruling out the possibility of a $CH_2CH=CMe_2$ substituent at the 2-position. Chiral stationary phase GC revealed enantiomer ratios that correspond to 97−100% inversion of configuration[18] at the lithium-bearing carbon, again analogous to the Still−Wittig rearrangement.[3]

Since the [2,3]-rearrangement shown in Scheme 2 is so facile, we briefly examined the possibility of executing such a [2,3]-rearrangement on (*N*-methyl pyrrolidino)stannane, as shown in Scheme 3. The alkylation affords a mixture of stereoisomers of the *N*-methyl-*N*-allylstannylpyrrolidinium bromides, as evidenced by NMR. Transmetalation and rearrangement is again facile, but the yield of rearrangement product is low. The low yield is probably due to the stereochemical requirements of the rearrangement: the nitrogen is now stereogenic, and only the diastereomer having the allyl group trans to the tin can rearrange. Further work on optimization of this transformation is in progress.

In conclusion, we have demonstrated that both [2,3] anionic and ylide rearrangements of unstabilized α-lithioamines occur with inversion of configuration at the metal-bearing carbon, that [1,2]- and [2,3]-mechanisms compete in the aza-Wittig rearrangement, and that the rearrangement of unstabilized nitrogen ylides is an extremely facile reaction that may have considerable synthetic potential.

Supporting Information Available: Details of the analysis of the rearrangement of deuterated 1 to 3, NMR data for compounds 1, 3, 4, 6, and 7, and general procedures for the rearrangements (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.
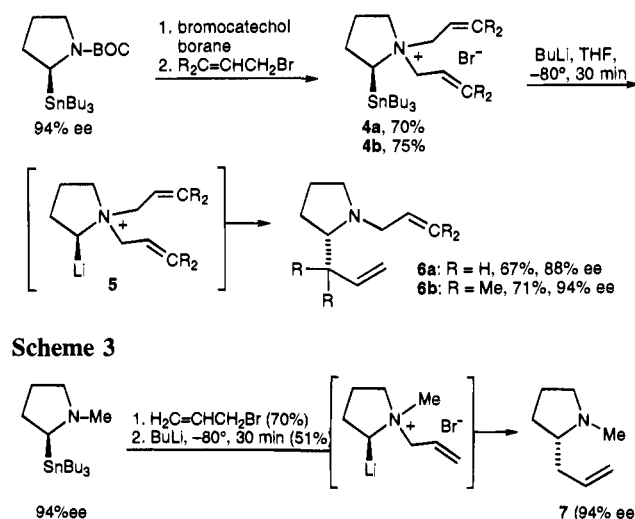
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(13) BOC-pyrrolidine was enantioselectively deprotonated and alkylated with allyl bromide to afford (*R*)-2-allyl-*N*-BOC-pyrrolidine in 27% yield. Removal of the BOC group and acylation with naphthoyl chloride gave *ent*-3.

(14) Inversion of configuration at the lithium-bearing carbon was observed in the Still−Wittig rearrangement as well.[3]
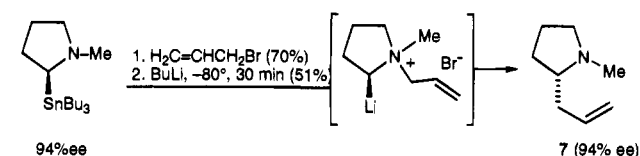
(15) It is known that in the (oxy) Wittig rearrangement, when [1,2]- and [2,3]-rearrangements compete, the latter predominate at low temperature and the former become increasingly important as the temperature is raised: (a) Baldwin, J. E.; DeBernardis, J.; Patrick, J. E. *Tetrahedron Lett.* **1970**, 353−356. (b) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1970**, 4−6. (c) Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556−3568.

(16) For complete details of the analysis, see the supporting information.

(17) We have previously noticed (see footnote 15 of ref 9) that racemic *N*-methyl-2-lithiopyrrolidine is more robust than the same compound of 94% ee.

(18) The absolute configuration of 6a was confirmed by conversion of 1 to 6a by Wittig rearrangement and alkylation with allyl bromide.