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Stereoselective [2,3]-Sigmatropic Rearrangements of Unstabilized Nitrogen Ylides[†]

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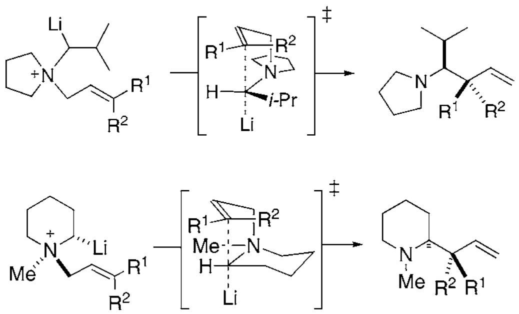
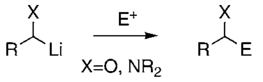
ABSTRACT

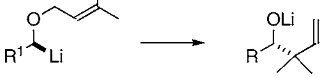


The steric course of the [2,3]-rearrangement of several unstabilized nitrogen ylides has been investigated. The reactions proceed cleanly through an *anti* transition state, affording modest to good yields of a single diastereomer of the product. In two examples containing an *N*-cinnamyl group, a competing [1,2]-rearrangement affords a minor product.

Electrophilic substitution reactions of α-alkoxy- and α-aminoorganolithium compounds (eq 1) have been extensively studied and constitute an important class of synthetic methods, with hundreds of applications reported so far.[1,2] A second class of carbon−carbon bond-forming reactions utilizing these reactive intermediates is sigmatropic rearrangements.[3,4] In 1978, Still and Mitra reported the first example of a [2,3]-rearrangement of an organolithium generated by tin−lithium exchange,[5] which was later shown to be invertive at the lithium-bearing carbon (eq 2).[6−8]



(1)



(2)

The nitrogen (aza) analogue of the Still−Wittig [2,3]-rearrangement (eq 3) is less facile, due primarily to the lower stability of the lithium amide compared to the lithium alkoxide product of the oxygen version.[3,4,9,10] Once generated,

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[†] Warmly dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

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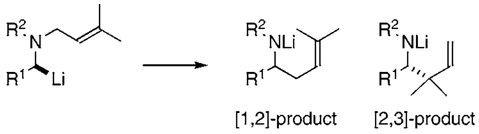
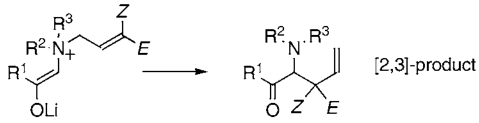
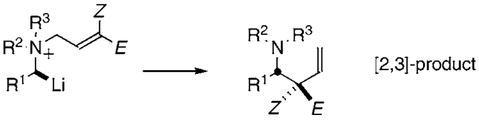
the *N*-allyl α-aminoorganolithium often follows competing [1,2]- and [2,3]-rearrangement pathways (eq 3).[11−13] Quaternization of the nitrogen (eq 4) with a trimethylsilyl group,[14] boron trifluoride,[15] or an alkyl group[13,16] accelerates the concerted [2,3]-rearrangement over the radical-mediated [1,2]-rearrangement of the ylides. The steric course of the anionic and ylide aza-[2,3]-rearrangements is invertive if the metal bearing carbon is stereogenic (eqs 3 and 5),[13] but the stereoselectivity at the migration terminus of nitrogen ylides has only been explored in stabilized ylides such as the enolate shown in eq 4. In most cases, the diastereoselectivity is modest,[16−18] with only a few examples of high selectivity in auxiliary mediated processes.[19,20] We now report the results of our studies on the diastereoselectivity at the migration terminus of the [2,3]-rearrangement of several unstabilized, lithio-nitrogen ylides (eq 5), in which we find that the rearrangement is highly stereoselective. *Note:* Strictly speaking, the ylide is the zwitterion having a positive nitrogen and a negative carbon. Since the anionic carbon is stereogenic, we draw the carbon−lithium ion pair as a bond.



(3)



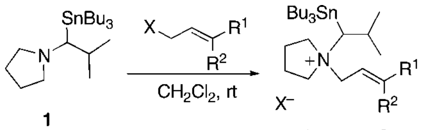
(4)



(5)

Stannane **1** is a challenging test of the methodology for two reasons. First, stannane **1** fails to undergo tin−lithium exchange, so it was of interest to determine whether quaternization of the nitrogen would facilitate the exchange. Second, we wanted to evaluate the diastereoselectivity of the [2,3]-rearrangement in the context of acyclic stereoselection. To test the first point, **1** was simply quaternized with methyl iodide. Treatment of the methiodide salt with butyllithium in THF at −78 °C for 1 h, quenching with methanol, and silica gel chromatography afforded a 69% yield of tetrabutyltin, indicating that transmetalation to the ylide is facile in this system. Quaternization of racemic **1** with *E*-crotyl bromide, and *E*- and *Z*-cinnamyl bromide affords ammonium salts **2a**−**c**, as shown in Scheme 1. For some compounds, anion exchange from halide to hexafluorophosphate facilitated handling, provided a salt that was less hygroscopic, and increased solubility in organic solvents (see the Supporting Information).

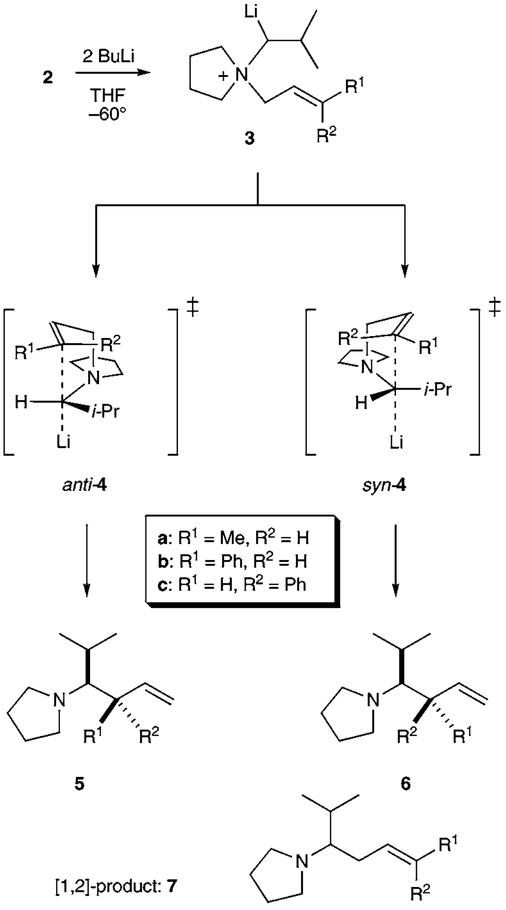
Scheme 1



1

2a: R^1 = Me, R^2 = H (95%)
2b: R^1 = Ph, R^2 = H (95%)
2c: R^1 = H, R^2 = Ph (87%)

Scheme 2



As illustrated in Scheme 2, stannylammonium ions **2a**−**c** were treated with butyllithium in THF at −60 °C to effect transmetalation and stirred at that temperature for 20−24 h.

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After workup and column chromatography, amines **5a**−**c** were obtained in the yields shown in Table 1, entries 1−3.

Table 1. Rearrangements of Ylides (Stannane + BuLi, −60 °C, unless Otherwise Noted)

entry	ylide	R^1	R^2	X^-	product(s)	yield (%)
1	**2a**	Me	H	I^-	**5a**	57
2	**2b**	Ph	H	PF_6^-	**5b**	54
3	**2c**	H	Ph	PF_6^-	**5c**	29
4	**10a**	Me	H	PF_6^-	**12a**	60
5[a]	**10b**	Ph	H	Br^-	**12b** + **14b** (4:1)	55
6[a]	**10c**	H	Ph	Br^-	**12c** + **14c** (9:1)	35

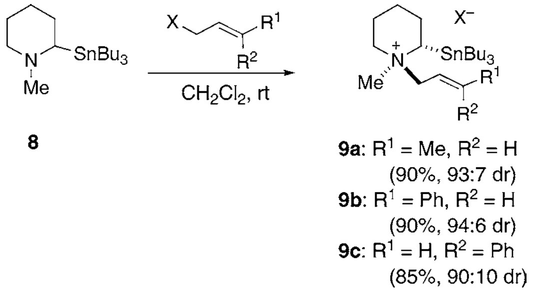
[a] *T* = −83 °C; MeLi instead of BuLi for transmetalation.

Of interest in these rearrangements is the possibility of two transition-state conformers, *syn* and *anti* **4a**−**c**, which would afford diasteromeric products **5** or **6**, and possibly [1,2]-rearrangement product **7**. In all cases, only one diastereomer was isolated. Independent synthesis of **5b** and **5c** established the relative configurations (see the Supporting Information). It appears that the [2,3]-rearrangement prefers the transition structure *anti*-**4**, independent of alkene geometry, even though *anti* **4c** having a *Z* double bond appears somewhat more congested. The lower yield from the *Z*-cinnamyl intermediate **3c** may indicate that steric crowding in the *anti* transition state slows the rearrangement, allowing pathways toward nonproductive decomposition to become more competitive; in this case, there were numerous unidentified polar byproducts. It is noteworthy that under these conditions, none of the [1,2]-products **7a**−**c** were detected.

If R^2 and R^3 in eq 5 are different, then the nitrogen is a stereocenter and the stereoselectivity of the rearrangement will rely on the stereoselective quaternization of the nitrogen. To probe the diastereoselectivity of the rearrangement in cyclic systems, we chose racemic *N*-methyl-2-(tributylstannyl)piperidine, **8**. Based on precedent from a single example in an earlier report,[13] we anticipated that alkylation of **8** would occur trans to the tin.

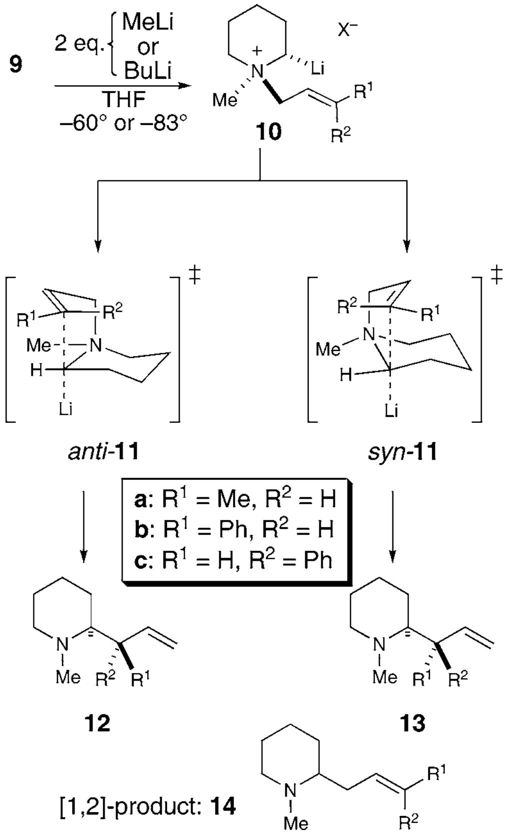
In the event, alkylation of **8** with *E*-crotyl bromide and with *E*- and *Z*-cinnamyl bromide afforded ammonium ions **9a**−**c**, with 90−94% diastereoselectivity, as indicated by integration of the *N*-methyl peaks in the NMR (Scheme 3).

Scheme 3



Again, exchange of the halide anion for PF_6^- often facilitated handling of the salt, increased its solubility in organic solvents and made it less hygroscopic.

Scheme 4



Transmetalation of **9a**−**c** afforded ylides **10a**−**c**, and ultimately their rearrangement products, as summarized in Table 1, entries 4−6, and illustrated in Scheme 4. The *E*-crotyl ylide **10a** rearranged to a mixture of isomers, of which piperidine **12a** was the major (92%) component. The isomers were not obtained in sufficient quantity to identify; one may be the [1,2]-product **14a**, while others are diastereomers that could have arisen from transition structure *syn*-**11** or from minor contaminants of cis alkene ylide (**10**, R^2 = Me, R^1 = H). *trans*-Cinnamyl ylide **10b** afforded a 3.6:1mixture of [2,3]-product **12b** and [1,2]-product **14b**, while *cis*-cinnamyl ylide **10c** afforded a 6.9:1 mixture of [2,3]-product **12c** and [1,2]-product **14c**. None of the diastereomeric products **13b**,**c** were detected by GC−MS, and the structure of **12b** was confirmed by independent synthesis (see the Supporting Information). To further confirm these assignments, stannane **8** was transmetalated with BuLi at −78 °C in THF and alkylated with *trans*-cinnamyl bromide according to our established procedure.[21] Analysis of the products revealed a 35:65 mixture of S_N2 product **14b**, and S_N2' product **12b**. In the rearrangement of **10b**,**c**, the extra stabilization afforded by the phenyl group probably facilitates

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homolytic cleavage of the allylic C−N bond to produce [1,2]-products **14b**,**c** after radical recombination. In summary, nitrogen ylides **3a**−**c** and **10a**−**c** rearrange preferentially through transition structures *anti*-**4** and *anti*-**11**, creating two adjacent stereocenters with a high degree of stereoselectivity. Further applications of the [2,3]-rearrangement of unstabilized nitrogen ylides are under active investigation and will be reported in due course.

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Supporting Information Available: Full experimental details, independent syntheses of **5b**, **5c**, and **12b**, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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