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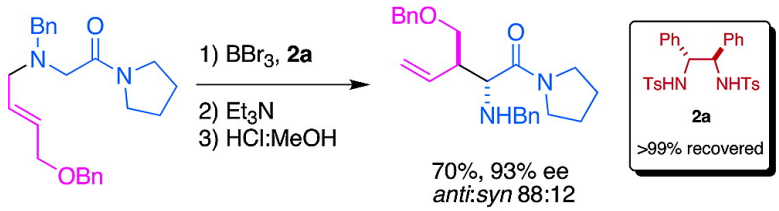

10 examples, 52-92% yield, up to 99% ee

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Asymmetric [2,3]-Sigmatropic Rearrangement of Allylic Ammonium Ylides

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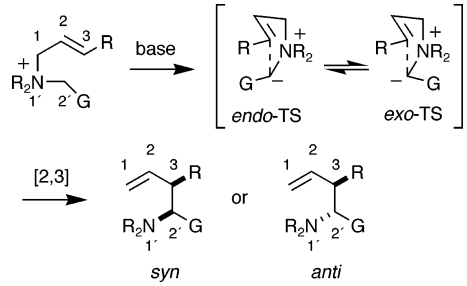
The [2,3]-sigmatropic rearrangement of allylic ammonium ylides has become a powerful strategy for the synthesis of nitrogen heterocycles.[1,2] The rearrangement is proposed to proceed via an envelope-like five-membered transition state, creating a C−C bond and at least one new stereogenic center (Scheme 1).[3] The relative stereochemical outcome is determined by steric and electronic interactions between the allyl moiety and the anion stabilizing group (G) in the *endo* and *exo* transition states. Asymmetric variants of this rearrangement have relied on intramolecular chirality transfer,[4] an elegant example being Sweeney's report of a highly diastereoselective rearrangement of various glycine-derived allylic ammonium salts using Oppolzer's chiral sultam as auxiliary.[5] Although it would be desirable to use chiral catalysts in these rearrangements, such strategies have been deemed problematic as the nitrogen atom must be quaternary, which seems to exclude coordination of the substrate to a chiral Lewis acid.[5]

We recently developed an efficient and highly *syn*-selective Lewis acid-mediated [2,3]-sigmatropic rearrangement of allylic ammonium ylides.[6,7] By NMR spectroscopy and computational methods, it was shown that the reaction proceeds through formation of an oxazaborolidine which, after deprotonation, rearranges into the corresponding homoallylic amine. As an extension of this investigation, we became interested in developing an asymmetric Lewis acid-mediated rearrangement and herein detail our results.

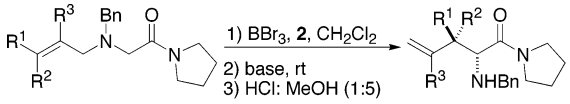
Initial attempts were directed toward identifying suitable chiral Lewis acids and optimal reaction conditions that would effect the rearrangement (Scheme 2 and Table 1). Thus, when using the diazaborolidine derived from BBr_3 and sulfonamide **2a** as Lewis acid[8] and phosphazene **4** as base,[9] **3a** was obtained in low yield and modest enantiomeric excess (entry 1). After some experimentation, it was found that optimal results were obtained with an excess[6] of the chiral Lewis acid and **4** (2 equiv of each), affording **3a** in 79% yield and 96% ee (entry 4).[10,11] It was also noted that Et_3N could be used instead of **4** without compromising the yield or enantiomeric excess (entry 5). Somewhat surprisingly, when the diazaborolidine derived from **2b** and BBr_3 was employed, homoallylic amine **3a** of opposite absolute configuration was obtained, with modest enantiomeric excess (entry 6).

With optimized rearrangement conditions at hand (Table 1, entry 5), substituted allylic amines **1b**−**f**,**h**−**k** were successfully transformed into homoallylic amines **3b**−**f**,**h**−**k** in good yields and good to excellent enantiomeric excesses (Table 2, entries 1−5, 7−10). (*E*)-Olefins **1b**, **1d**, **f**, and **h** gave mainly the *anti*-isomer (entries 1, 3, 5, 7), while (*Z*)-olefins **1c**,**e**,**i** favored the *syn*-diastereomer (entries 2, 4, 8). In this series, cinnamylamines **1h**,**i** rearranged with disappointingly poor diastereoselectivities, the reasons for which are not clear. Subjecting (*Z*)-vinylsilane **1g** to the reaction conditions gave the [1,2]-rearranged product **5** (72%, 61% ee, entry 6), probably for steric reasons (vide supra). The sterically demanding trisubstituted olefin **1j** and 2-methylpropenyl derivative **1k** rearranged to give the corresponding products **3j** and **3k**, respectively, with excellent enantioselectivities (entries 9, 10).

Scheme 1. The [2,3]-Sigmatropic Rearrangement of Ammonium Ylides (R = alkyl, G = anion-stabilizing group)

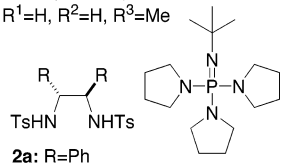


Scheme 2. Asymmetric [2,3]-Sigmatropic Rearrangement of **1**



1a R^1,R^2,R^3=H,H,H
1b R^1=Me, R^2=H, R^3=H
1c R^1=H, R^2=Me, R^3=H
1d R^1=CH_2OBn, R^2=H, R^3=H
1e R^1=H, R^2=CH_2OBn, R^3=H
1f R^1=$SiPhMe_2$, R^2=H, R^3=H
1g R^1=H, R^2=$SiPhMe_2$, R^3=H
1h R^1=Ph, R^2=H, R^3=H
1i R^1=H, R^2=Ph, R^3=H

1j R^1=Me, R^2=Me, R^3=H **3**
1k R^1=H, R^2=H, R^3=Me



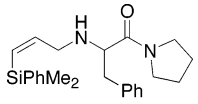
2a: R=Ph
2b: R=-$(CH_2)_4$-

4

Table 1. Optimization of the Asymmetric [2,3]-Sigmatropic Rearrangement of **1a**[a]

entry	ligand/equiv	BBr_3 (equiv)	base/equiv	yield of **3a** (%)[b]	ee (%)[c]
1	**2a**/1.2	1.4	**4**/1.0	22 (55)	85 (*R*)
2	**2a**/1.2	1.2	**4**/2.0	39 (59)	97 (*R*)
3	**2a**/2.0	2.0	**4**/1.0	18 (78)	97 (*R*)
4	**2a**/2.0	2.0	**4**/2.0	79 (0)	96 (*R*)
5	**2a**/2.0	2.0	Et_3N/5.0	87 (3)	97 (*R*)
6	**2b**/2.0	2.0	**4**/2.0	87 (0)	28 (*S*)

[a] For experimental conditions, see Supporting Information. [b] Yield determined by HPLC. Yield of recovered starting material is in parentheses. [c] For determination of enantiomeric excess and absolute configuration, see Supporting Information.



5

The stereochemical outcome in this rearrangement can be rationalized as follows (Scheme 3). Reaction of **1b** with the chiral Lewis acid gives the corresponding oxazaborolidines that, after deprotonation, afford structures **A** and **B**.[12] [2,3]-Rearrangement from *exo* isomer **A** then proceeds readily to give the major product

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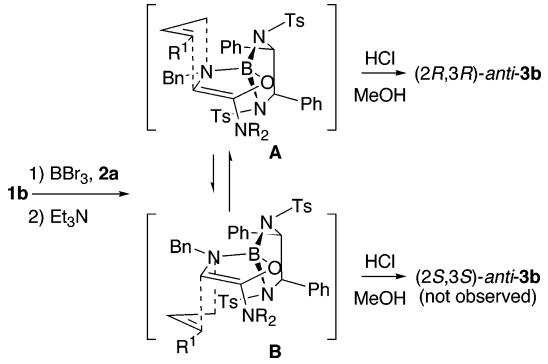
Table 2. Asymmetric [2,3]-Sigmatropic Rearrangement of Amines **1**[a]

entry	amine	yield (%)[b]	*anti*:*syn*[c]	ee (%)[d] *anti*:*syn*
1	**1b**	**3b**/82	79:21	96 (2*R*,3*R*):75 (2*R*,3*S*)[e]
2	**1c**	**3c**/85	20:80	82 (2*R*,3*R*):98 (2*R*,3*S*)[e]
3	**1d**	**3d**/70	88:12[f]	93:n.d.[f,g]
4	**1e**	**3e**/71	29:71[f]	98:99[f]
5	**1f**	**3f**/52	95:5[f]	99:n.d.[f,g]
6	**1g**	*h*		
7	**1h**	**3h**/92	67:33	97:77[f]
8	**1i**[i]	**3i**/65[j]	30:70	94:88[f]
9	**1j**	**3j**/64		96[f]
10	**1k**	**3k**/80		99[f]

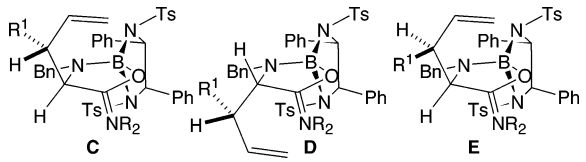
[a] For experimental conditions, see Supporting Information. [b] Isolated yield of diastereomeric mixture. [c] Determined by ^{1}H NMR analysis of the crude product. [d] For determination of enantiomeric excess, see Supporting Information. [e] The absolute configuration was established via chemical correlation; see Supporting Information. [f] Stereochemistry assigned by analogy with the rearrangements of **1b**. [g] n.d. = not determined. [h] Gave **5** in 72% yield and 61% ee. [i] *E*:*Z* 1:10, reaction run at −20 °C. [j] With 14% recovered starting material.

Scheme 3. Kinetically Controlled Stereoselection in the Rearrangement of **1b**



(2*R*,3*R*)-*anti*-**3b** (R^1 = Me). Reaction of **B** is disfavored due to steric interactions between the allyl moiety and the adjacent *N*-Ts group, and **B** will thus isomerize to **A** followed by rearrangement.[13] In this scenario, (2*R*,3*S*)-*syn*-**3b** is formed from the *endo* complex corresponding to **A**, which should experience a destabilizing interaction between the internal vinylic *C*-H moiety and the proximal sulfonamide moiety, thus accounting for the observed *anti*:*syn*-selectivity. This also explains the results with **1g**; both the *exo* and *endo* complexes corresponding to **A** will experience severe steric interactions, and consequently, the [1,2]-rearrangement affording **5** becomes the favored pathway.

In contrast to this kinetically controlled stereoselection, a thermodynamic pathway can be envisioned. Formation of **A** and **B** followed by rearrangement will give oxazaborolidines **C** and **D**, respectively. Of these, **C** is thermodynamically favored, and its hydrolysis will give (2*R*,3*R*)-*anti*-**3b** (R^1 = Me).[14] Equilibration of **D** under the basic reaction conditions results in **E** that after work up will afford (2*R*,3*S*)-*syn*-**3b** (R^1 = Me). In this scenario, the *anti*:*syn*-selectivity is controlled by the initial rate for the formation of **A** and **B**, while the absolute stereochemistry at C2 in the product is dictated by the chiral ligand. Attempts to verify this reaction pathway by subjecting complexes **C** and **D** to D_2O before workup resulted in no deuterium incorporation, the reason for which we are currently favoring the mechanism outlined in Scheme 3.



In conclusion, we have developed the first asymmetric Lewis acid-mediated [2,3]-sigmatropic rearrangement of allylic ammonium ylides. We are currently investigating the scope of this transformation as well as its application in total synthesis, and the results will be presented in due course.

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

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(9) Care must be taken in order to exclude the formed HBr; see Supporting Information.
(10) The ligand could be recovered almost quantitatively; see Supporting Information.
(11) Other solvents (Et_2O, THF, or PhMe) did not improve the yield or enantiomeric excess.
(12) The corresponding *endo* complexes are omitted for clarity.
(13) Equilibration of diastereomeric oxazaborolidines has been described previously, see: Vedejs, E.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3028−3034. Equilibration before deprotonation and rearrangement can also be envisioned.
(14) Oxazaborolidine **C** (R^1 = H) is 10 kcal/mol more stable than **D** (R^1 = H) at the B3LYP/6-31G* level of calculation. For computational details, see Supporting Information.

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