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Lewis acid mediated [2,3]-sigmatropic rearrangement of allylic ammonium ylides

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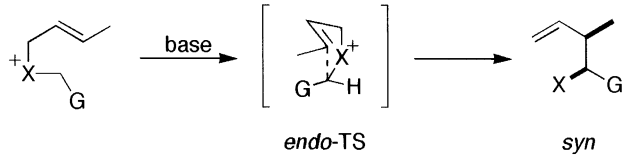
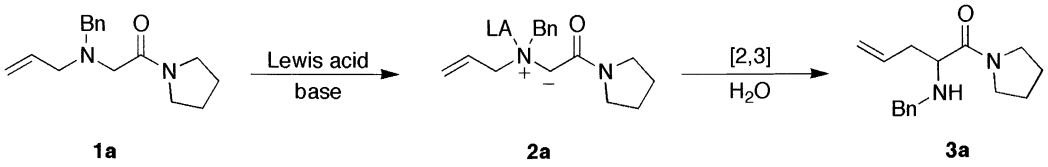
Abstract—An investigation of the Lewis acid mediated [2,3]-sigmatropic rearrangement of allylic ammonium ylides has been conducted by employing various bases and boron Lewis acids. Using BBr_3 together with the phosphazene base **6**, various allylic amines could be rearranged in good yields with low to excellent diastereoselectivity.

The [2,3]-sigmatropic rearrangement of ylides has proven to be a versatile tool for regio- and stereoselective transformations.[1] The advantages with this type of reaction are the formation of a carbon–carbon bond in exchange for a carbon-heteroatom bond and the possibility of high stereoselection at the newly introduced stereogenic centers. The stereoselectivity observed in the rearrangement can be rationalized by invoking a cyclic envelope-like five-membered transition state (Scheme 1, one possible TS shown).[2] The most commonly used ylides are those from amines and sulfides, although there are reports of oxonium,[3] selenonium[4] and even halonium ylides.[5] The [2,3]-sigmatropic rearrangement of sulphonium ylides generally gives the corresponding product in high stereoselectivity and have been used as a key step in several synthetic schemes.[1] In contrast, the [2,3]-sigmatropic rearrangement of ammonium ylides has not enjoyed equal popularity in organic synthesis, although it has been thoroughly investigated.[1,6] The reasons for this are probably the low stereoselectivity often obtained in the rearrangement, especially for acyclic substrates,[1] and the formation of a tertiary amine, which is not amenable to further derivatization unless *N*-protecting groups are incorporated (Scheme 1, X = NRR^1, R = alkyl, R^1 = protecting group).



Scheme 1. The [2,3]-sigmatropic rearrangement of ylides (X = SR or NRR^1; G = activating group, e.g. COOMe, CN, C≡CTMS).

To circumvent these disadvantages, allylic ammonium ylides generated from Lewis acid complexed amines could be used as substrates in the [2,3]-sigmatropic rearrangement.[7] It was hoped that such a protocol would allow for fine tuning of the reactivity of the ylide and the stereoselectivity in the reaction by choice of Lewis acid. Also, the product from the rearrangement would be a secondary amine and thus suitable for further transformations (see Scheme 2). Herein we wish to report the results of the preliminary investigation of



Scheme 2. The Lewis acid mediated [2,3]-sigmatropic rearrangement of **1a** (LA = Lewis acid).

Keywords: [2,3]-sigmatropic rearrangement; ammonium ylide; Lewis acid.

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Table 1. BF_3-assisted rearrangement of **1a**[a]

Entry	$BF_3{\cdot}OEt_2$ (equiv.)	Base/(equiv.)	T (°C)/t (h)	Yield of **3a** (%)[b]
1	1.5	LDA/1.5	−78→rt/2.5	0 (92)[c]
2	3.0	KHMDS/3.0	−20/23	4 (42)
3	2.8	KHMDS/2.8[d]	−20/19.5	4 (94)
4	1.2	KHMDS/1.2[e]	−20/20	12 (63)
5[f]	1.2	*i*-Pr_2NEt/1.2	Reflux/13	57 (15)

[a] Reaction conditions: To **1a** in THF at −78°C was added $BF_3{\cdot}OEt_2$ and base.
[b] Yields determined by HPLC. Yield of recovered starting material in parenthesis.
[c] Crude yield.
[d] 2.9 equiv. 18-crown-6 was added.
[e] 1.2 equiv. 18-crown-6 was added.
[f] PhMe used as solvent.

the role of Lewis acids and bases in the [2,3]-sigmatropic rearrangement of amines.

Initial experiments were designed to probe the effect of various bases on the rearrangement using $BF_3{\cdot}OEt_2$ as Lewis acid, which has been shown to preferentially coordinate to the nitrogen nucleus in amino acid derivatives.[8]

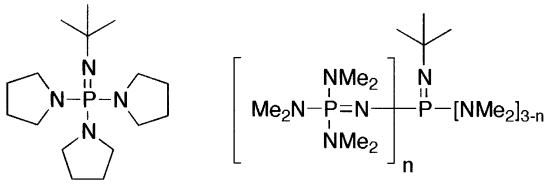
Thus, forming **2a** (LA = BF_3) by mixing **1a** and $BF_3{\cdot}OEt_2$ followed by addition of LDA or KHMDS gave only a low or no yield of **3a** (Table 1, entries 1–3).[9] After considerable experimentation it was found that treating **1a** with equimolar amounts of $BF_3{\cdot}OEt_2$, KHMDS and 18-crown-6 gave **3a** in a modest 12% yield (entry 4). Surprisingly, it was found that the rearrangement was promoted by *i*-Pr_2NEt in refluxing toluene, affording **3a** in 57% yield (entry 5). Although elevated reaction temperatures were needed for the transformation, the result suggested that stronger nonionic bases could be employed at a lower reaction temperature.

The commercially available phosphazene bases recently developed by Schwesinger seemed to be appropriate bases for this purpose (Fig. 1).[10] Treating **2a** (LA = BF_3) with the phosphazene bases **4** and **5** gave similar yields of **3a** as the rearrangements with the amide-bases (Table 2, entries 1 and 2), while the stronger base **6** gave a substantial increase in yield. Treating **2a** (LA = BF_3) with **6** at −20°C overnight afforded **3a** in 35% yield (entry 3), and performing the reaction at room temperature gave **3a** in 42% yield (entry 4). Although the yields of **3a** were lower than with *i*-Pr_2NEt, the rearrangement could be run at lower temperatures.

These encouraging results prompted us to investigate the influence of Lewis acidity upon the rearrangement. Hence, by employing various boron halides a direct comparison between reactivity and Lewis acidity could be made. Indeed, the stronger Lewis acids BCl_3 and BBr_3 increased the yield of **3a** (entries 5 and 6), indicating a need for a strong Lewis acid to promote the [2,3]-sigmatropic rearrangement.[11]

Having developed useful reaction conditions for the rearrangement of **1a**, other substrates were designed to investigate the stereoselectivity of the rearrangement. Hence, allylic amines **1b–e** were synthesized and treated with BBr_3 and phosphazene base **6**.[12] Under the optimized reaction conditions (Table 3) the (*E*)-substrates **1b** and **c** could be rearranged with excellent diastereoselectivity and in good yield, affording 71% of *syn*-**3b**:*anti*-**3b** in >20:1 ratio (Table 3, entry 1) and 62% of *syn*-**3c**:*anti*-**3c** in 11:1 ratio (entry 2).[13] The (*Z*)-substrate **1d** on the other hand rearranged with low selectivity, giving 56% of *syn*-**3d**:*anti*-**3d** in 6:5 ratio (entry 3). To further validate the rearrangement, the trisubstituted olefin **1e** was exposed to the reaction conditions, yielding 60% of **3e** (entry 4).

Next, substrates with different anion activating groups were probed. Employing the reaction conditions on the *tert*-butyl ester **7** gave a mixture of unwanted side-



BTPP (**4**); pK_{BH+}=~26

P_2-t-Bu (**5**): n=1; pK_{BH+}=~33
P_4-t-Bu (**6**): n=3; pK_{BH+}=~42

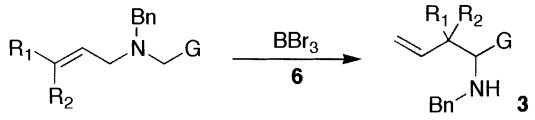
Figure 1. The Schwesinger phosphazene bases.

Table 2. Base and Lewis acid optimization of the rearrangement of **1a**[a]

Entry	Lewis acid	Base	T (°C)/t (h)	Yield of **3a** (%)[b]
1	$BF_3{\cdot}OEt_2$	**4**	−20/20	11 (62)
2	$BF_3{\cdot}OEt_2$	**5**	−20/19	12 (78)
3	$BF_3{\cdot}OEt_2$	**6**	−20/20	35 (65)
4	$BF_3{\cdot}OEt_2$	**6**	rt/20	42 (50)
5	BCl_3	**6**	−20/16	46 (40)
6	BBr_3	**6**	−20/16	66 (22)

[a] Reaction conditions: To **1a** (1.0 equiv.) in PhMe at −78°C was added Lewis acid (1.2 equiv.) and base (1.2 equiv.).
[b] Yields determined by HPLC. Yield of recovered starting material in parenthesis.

Table 3. [2,3]-Sigmatropic rearrangements of **1b–e**[a]



Entry	Substrate	R^1	R^2	G	Yield of **3** (%)[b]	*Syn*:*anti*[c]
1	**1b**	Me	H	$CONC_4H_8$	71 (20)	>20:1
2	**1c**	Ph	H	$CONC_4H_8$	62 (32)	11:1
3	**1d**	H	Me	$CONC_4H_8$	56 (33)	6:5
4	**1e**	Me	Me	$CONC_4H_8$	60 (31)	–
5	**7**	H	H	CO_2t-Bu	–[d]	–
6	**8**	H	H	CCTMS	n.r.[e]	–

[a] Reaction conditions: To a substrate (1.0 equiv.) in PhMe at −78°C was added BBr_3 (1.1 equiv.) and **6** (1.0 equiv.). Stirred overnight (18–20 h) at −20°C.
[b] Yield of recovered starting material in parenthesis.
[c] Ratio determined by ^1H NMR.
[d] No product could be detected, instead the acid of **7** and *N*-allylbenzylamine together with unidentified side products were formed.
[e] n.r. = no reaction.

products (Table 3, entry 5). Having a TMS-protected propargyl group as an activating group gave no reaction and instead starting material **8** was recovered (entry 6).

In the rearrangement of **1** the absence of any product arising from the competing [1,2]-radical process indicates that the BBr_3 mediated reaction proceeds by a [2,3]-sigmatropic pathway. The stereochemical outcome in the rearrangement of **1** will most likely depend on the relative orientation of the *N*-coordinated Lewis acid and the amide enolate moiety in the transition states leading to *syn*- and *anti*-**3**. However, further studies are required before a reasonable rationale can be provided.

In conclusion, the Lewis acid mediated [2,3]-sigmatropic rearrangement of allylic ammonium ylides has been optimized by use of non-ionic phosphazene bases rather than traditional amide or carbanionic bases. The effect of Lewis acidity was investigated and the reactivity of BBr_3 in promoting the rearrangement proved superior to $BF_3{\cdot}OEt_2$. Several substrates were probed showing the BBr_3 mediated [2,3]-sigmatropic rearrangement to proceed with good yields and diastereoselectivities using a tertiary amide as an anion activating group.

Acknowledgements

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12. *Representative procedure: rearrangement of **1b***. To a stirred solution of **1b** (35 mg, 0.13 mmol) in toluene (1.5 mL) at −78°C was added BBr_3 (0.15 mmol). To the resultant solution was added P_4-*t*-Bu (0.13 mmol) and the mixture was allowed to reach −20°C. After stirring for 19 h the reaction was quenched with 2 M HCl (1 mL) and allowed to stir for one hour at rt. The solution was made alkaline with 2 M NaOH (1.5 mL) and the resultant mixture filtered through an Extrelut® NT3 tube, which was eluted with CH_2Cl_2 (15 mL). The concentrated residue was chromatographed (MeCN:Et_2O 0:1→1:0) to provide *syn*-**3b** (25 mg, 71%, ds>20:1). ^{1}H NMR ($CDCl_3$, 500 Mz) δ_H 7.34 (d, 2H, $J=7.1$), 7.30 (t, 2H, $J=7.1$), 7.22 (t, 1H, $J=7.1$), 5.79 (ddd, 1H, $J=17.2$, 10.3, 7.3), 5.05 (d, 1H, $J=17.2$), 4.96 (d, 1H, J = 10.3), 3.85 (d, 1H, $J=13.4$), 3.54 (d, 1H, $J=13.4$), 3.54 (m, 1H), 3.42 (dt, 1H, $J=12.0$, 6.6), 3.27 (m, 1H), 3.12 (m, 1H), 3.11 (d, 1H, $J=7.3$), 2.38 (sextet, 1H, $J=7.3$), 2.20 (bs, 1H), 1.88–1.77 (m, 4H), 1.12 (d, 3H, $J=7.3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 172.8, 140.7, 140.3, 128.2, 128.2, 126.8, 114.7, 63.1, 52.1, 46.2, 45.5, 41.4, 26.0, 24.2, 15.9.
13. The relative stereochemistry of the secondary amines **3** was determined by Hg^{2+}-cyclization to the corresponding pyrrolidines followed by NOE interactions measurements.