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Lewis Acid Mediated Asymmetric [2,3]-Sigmatropic Rearrangement of Allylic Amines. Scope and Mechanistic Investigation

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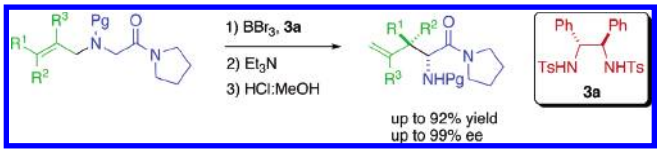
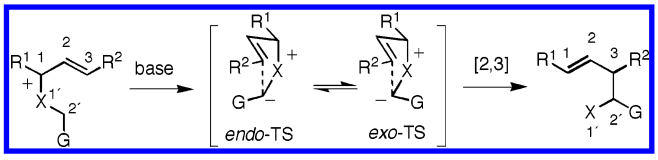


The first asymmetric [2,3]-sigmatropic rearrangement of achiral allylic amines has been realized by quaternization of the amines with an enantiomerically pure diazaborolidine and subsequent treatment with Et_3N. The resultant homoallylic amines were obtained in good yields and excellent ee's. The observed diastereo- and enantioselectivities were rationalized by invoking a kinetically controlled process, and support for this model was obtained from an NMR spectroscopic investigation of the chiral Lewis acid−substrate complex. The structure of the Lewis acid−product complex was established by X-ray crystallographic analysis and supported the proposed mechanism.

Introduction

Carbon−carbon bond-forming reactions are of central importance to the organic chemist, and of particular interest are those transformations that proceed with high regio- and stereoselectivity. Although many such reactions have been successfully developed, pursuit of asymmetric versions is still a challenging goal. In this respect, the [2,3]-sigmatropic rearrangement of allylic onium salts (Scheme 1),[1−3] such as ammonium,[4,5] sulfonium,[6] oxonium,[3,7] selenonium,[8] and iodonium salts,[5,9] have been investigated, establishing the rearrangement as a powerful C−C bond-forming reaction. The rearrangement is believed to proceed via a five-membered cyclic transition state,[10,11] and the stereochemical outcome is dependent on steric and electronic interactions between the migrating allyl moiety and the anion-stabilizing group (G, Scheme 1) in the exo and endo transition states.[1]

SCHEME 1. [2,3]-Sigmatropic Rearrangement of Ylides[a]



[a] Key: R, R′ = alkyl, Ar. X = NR_2^2, SR^2, OR^2, SeR^2, I. G = Ar, CO_2Me, CN, CCTMS.

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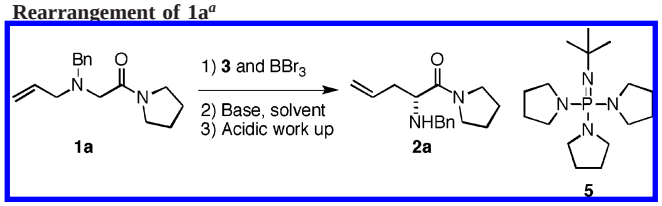
TABLE 1. Optimization of the Asymmetric [2,3]-Sigmatropic Rearrangement of 1a[a]

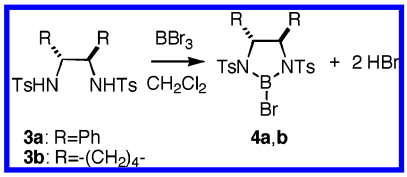


entry	ligand/ (equiv)	BBr_3/ (equiv)	base/ (equiv)	solvent	conversion of **2a** (%)[b]	ee (%)[c]
1[d]	**3a**/2.0	2.4	**5**/1.0	PhMe	29(~30[e])	68 (*R*)
2[f]	**3a**/1.2	1.4	**5**/1.0	CH_2Cl_2	22(55)	85 (*R*)
3[f]	**3a**/1.2	1.4	Et_3N/1.0	CH_2Cl_2	17(59)	69 (*R*)
4[f]	**3a**/1.2	1.4	Et_3N/3.0	CH_2Cl_2	43(32)	89 (*R*)
5[f]	**3a**/1.2	1.4	K_2CO_3/5.0	CH_2Cl_2	0(83)	–
6[f]	**3a**/1.2	1.4	$NaHCO_3$/12	CH_2Cl_2	0(83)	–
7	**3a**/1.2	1.2	**5**/2.0	CH_2Cl_2	39(59)	97 (*R*)
8	**3a**/1.2	2.0	**5**/2.0	CH_2Cl_2	79(0)	48 (*R*)
9	**3a**/2.0	2.0	**5**/2.0	CH_2Cl_2	79(0)	96 (*R*)
10[g]	**3a**/2.0	2.0	**5**/2.0	CH_2Cl_2	71(11)	97 (*R*)
11	**3a**/2.0	2.0	**5**/1.0	CH_2Cl_2	18(78)	97 (*R*)
12	**3a**/2.0	2.0	**5**/2.0	PhMe	70(30)	96 (*R*)
13[h]	**3a**/2.0	2.0	**5**/2.0	Et_2O	27(33)	96 (*R*)
14	**3a**/2.0	2.0	**5**/2.0	THF	15(83)	84 (*R*)
15	**3a**/2.0	2.0	Et_3N/5.0	CH_2Cl_2	87(3)	97 (*R*)
16	**3b**/2.0	2.0	Et_3N/5.0	CH_2Cl_2	84(0)	25 (*S*)
17	**3b**/2.0	2.0	**5**/2.0	CH_2Cl_2	87(nd)	28 (*S*)

[a] Reaction conditions: to a premade solution of **4a** at room temperature was added **1a** (1 equiv), and the resultant solution was stirred for 1 h. The base was added, and the reaction mixture was stirred for 18−22 h, unless otherwise stated. [b] Conversion determined by HPLC. Unreacted **1a** in parentheses. [c] Determined by HPLC analysis of the crude product on a Chiracel OJ column (hexane/^{i}PrOH). The absolute configuration was established via chemical correlation; see ref 14. [d] Reaction performed at −20 °C. [e] Estimated from ^{1}H NMR spectroscopy. [f] Reaction was run for 3 days. [g] Reaction was run for 3 h. [h] Reaction was run for 40 h.

A salient feature of the [2,3]-sigmatropic rearrangement is that two new vicinal stereocenters can be created (C2′ and C3, see Scheme 1). Furthermore, the olefin moiety and the anion-stabilizing group provide possibilities for further derivatization, thus turning the rearrangement into a useful tool in the construction of complex organic compounds. An inherent drawback in the [2,3]-sigmatropic rearrangement of ylides is that the heteroatom moiety in the resultant product is fully substituted, making further transformations of this moiety problematic. Asymmetric variants of this rearrangement have typically relied on intramolecular chirality transfer, either via chirality transfer within the cyclic transition state or by auxiliary control.[1,2,12] An elegant example of the latter type is Sweeney's report of a highly diastereoselective rearrangement of various glycine-derived allylic ammonium salts using Oppolzer's sultam.[13] 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.[13] To address this issue, a [2,3]-sigmatropic rearrangement of ammonium ylides was designed in which the ylid was generated by complexation with a Lewis acid.[15] Having realized this, our attention was directed toward the possibility of employing chiral Lewis acids, and recently, we communicated the first asymmetric [2,3]-sigmatropic rearrangement of achiral allylic amines mediated by a chiral diazaborolidine.[14] The transformations proceeded in good yields and provided various secondary homoallylic amines with moderate to good diastereoselectivities and excellent ee's; a rationalization of the observed selectivities was also presented.[15,16] It was envisaged that either a kinetically or thermodynamically controlled process was responsible for the stereochemical outcome. Herein, we report the full details of this investigation.

SCHEME 2. Preparation of the Chiral Lewis Acids 4a,b



Results and Discussion

The optimization of the asymmetric rearrangement of **1** mediated by **4a**,**b** is summarized in Table 1.

The initial attempts to effect an asymmetric rearrangement were performed by mixing the chiral ligand **3a** and BBr_3 to generate Lewis acids **4a** (Scheme 2).[17] Subsequent removal of the solvent and the formed HBr under a vacuum was followed by addition of **1a**, and after 1−2 h, the resultant **1a**/**4a** complex was treated with base. When a solution of amine **1a** in PhMe was added to **4a**, a precipitate was formed, which prevented efficient stirring of the reaction mixture. Although promising results were obtained in this solvent (Table 1, entry 1), changing to CH_2Cl_2 avoided this problem and resulted in a homogeneous solution throughout the reaction. Consequently, employment of 1.2 equiv of **3a** and 1.4 equiv of BBr_3 together with phosphazene base **5** in CH_2Cl_2 furnished **2a** with high ee, although the yield was still low (entry 2). Using instead a stoichiometric amount of Et_3N as base gave a comparable yield but a slight decrease in ee (entry 3), and it was shown that an excess of Et_3N was advantageous, producing **2a** in 43% yield and with high ee (entry 4). The weaker bases K_2CO_3 and $NaHCO_3$ did not promote the rearrangement (entries 5 and 6). Surprisingly, the ee's obtained in the rearrangement were inconsistent, regardless of the amount or type of base employed,[18] and this irregularity was attributed to the slight excess of BBr_3 used in the preparation of Lewis acid **4a**.[19] Because BBr_3 is a stronger Lewis acid than **4a**, amine **1a** will preferentially complex to BBr_3 and react through an achiral pathway, thus lowering the obtained ee. Consequently, by using an equimolar amount of BBr_3, we obtained an excellent

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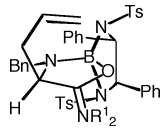
(18) The rearrangements were repeated but gave differing ee's.

(19) Excess BBr_3 was trapped as BBr_4 anions during preparation of the chiral Lewis acid.



6

FIGURE 1. Structure of complex **6**.

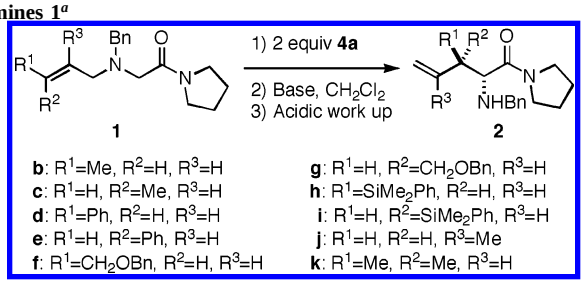
ee, although the conversion was still moderate (entry 7). Likewise, employment of a large excess of BBr_3 significantly lowered the ee, although the conversion of **1a** was complete (entry 8). Although the ee of the rearrangement was gratifying, the low conversion had to be addressed. This issue could be solved by adding 2 equiv of the Lewis acid **4a** to **1a** in CH_2Cl_2 at room temperature, adding 2 equiv of base **5**, and stirring the resultant mixture overnight. These reaction conditions satisfactorily afforded **2a** in 79% yield and with excellent ee (entry 9).

In the initial experiments, an unidentified byproduct could be observed via ^{1}H NMR spectroscopy, which proved to be compound **6**, the complex between the product from the rearrangement and the Lewis acid (Figure 1). When subjecting the crude reaction mixture to saturated $NaHCO_3$ followed by chromatography, we could isolate complex **6** in 93% yield. Recrystallization of this material followed by X-ray crystallographic analysis established the structure of **6** and, consequently, the absolute configuration of **2a** (see Supporting Information). The complex was shelf-stable for at least several months.

Consequently, it was decided to run the reaction overnight because it was not complete after 3 h (entry 10). Furthermore, it was evident that an excess of base was required; applying 1 equiv of base gave a poor conversion of **1a** (entry 11). Using PhMe as solvent with the optimized reaction conditions gave comparable results (entry 12), but Et_2O and THF gave lower yields and/or ee's (entries 13 and 14). As expected, an excess of Et_3N could be employed as base without compromising yield or ee (entry 15). By using the chiral Lewis acid **4b**, derived from the ligand **3b**, we obtained good yields of *ent*-**2a**. However, the ee's were poor, and the product had the opposite absolute configuration (entries 16 and 17).

With optimized rearrangement conditions at hand, the focus was turned to examine the scope and limitations of the asymmetric rearrangement as well as to establish a stereochemical rationale accounting for the observed outcome. A series of allylic amines were selected to reflect different electronic properties and the steric bulk of the allyl moiety (Table 2). Four different (*E*)/(*Z*)-olefin pairs (**1b**−**i**) were prepared as the anti/syn selectivity obtained in the rearrangements of such pairs might provide valuable information about steric and electronic factors effecting the transition state. As an additional advantage, silyl-substituted olefins **1h** and **1i** would furnish interesting products containing an allylsilane moiety. The (*E*)-olefin **1b** gave a smooth rearrangement under the optimized conditions, affording 82% of **2b** in a 79:21 anti/syn ratio and an excellent ee of the major diastereomer (Table 2, entry 1). An attempt to improve the selectivity by performing the reaction at −20 °C resulted in a low conversion (entry 2). Using PhMe as solvent gave poorer diastereoselectivity and low conversion of **1b** (entry 3). The isomeric (*Z*)-olefin **1c** gave the opposite major diastereomer, *syn*-**2c**, with a similar ee and an almost identical but reversed anti/syn ratio (20:80, entry 4). Pursuing the asymmetric rearrangement with the (*E*)/(*Z*)-isomeric pair of cinnamyl amines **1d**,**e** and the benzyloxy methylene olefins **1f**,**g** provided the

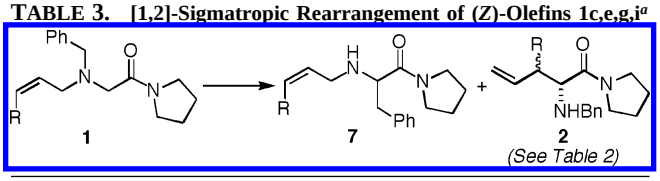
TABLE 2. Asymmetric [2,3]-Sigmatropic Rearrangement of Amines 1[a]



entry	amine	yield (%)[b]	anti/syn[c]	ee anti/ee syn (%)[d]
1	**1b**	**2b** 82	79:21	96 (2*R*,3*R*):75 (2*R*,3*S*)[e]
2	**1b**	**2b** *46*[f]	80:20	96 (2*R*,3*R*):nd[e,g]
3	**1b**	**2b** *<10*[h]	67:33	nd
4	**1c**	**2c** 85	20:80	82 (2*R*,3*R*):98 (2*R*,3*S*)[e]
5	**1d**	**2d** 92	67:33	97:77[i]
6	**1e**[j]	**2e** 57[k]	37:63	92:93[i]
7	**1e**[j]	**2e** 65[f,l]	30:70	94:88[i]
8	**1f**	**2f** 70	88:12[i]	93:nd[g,i]
9	**1g**	**2g** 71	29:71[i]	98:99[i]
10	**1h**	**2h** 52	95:5[i]	99:nd[g,i]
11	**1i**	**7i** 72[m]	−	61
12	**1j**	**2j** 80	−	99[i]
13	**1k**	**2k** 64	−	96[i]

[a] Reaction conditions: to a premade solution of **4a** (2 equiv) at room temperature was added **1** (1 equiv), and the resultant solution was stirred for 1 h. Et_3N (5 equiv) was added, and the reaction mixture was stirred for 18−22 h. [b] Isolated yield of the diastereomeric mixture. Conversions in *italics*. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] Determined by HPLC analysis of crude products; see ref 14. [e] The absolute configuration was established via chemical correlation; see ref 14. [f] The reaction was performed at −20 °C. [g] nd = not determined. [h] The reaction was performed in PhMe. [i] Stereochemistry assigned by analogy with the rearrangements of **1b**. [j] *E*/*Z* 1:10. [k] A byproduct was formed; see Table 3. [l] 14% recovered **1e**. [m] See Table 3.

TABLE 3. [1,2]-Sigmatropic Rearrangement of (*Z*)-Olefins 1c,e,g,i[a]



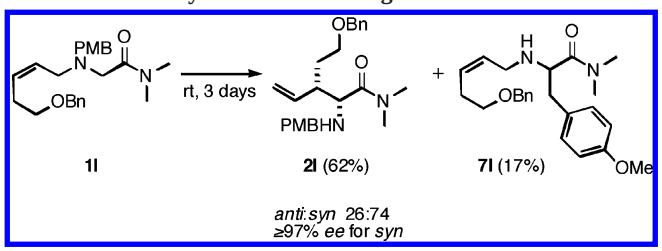
			conversions (%)[b]	
entry	amine	*T* (°C)	**7**	**2**
1	**1i** (R = $SiMe_2Ph$)	rt	∼100[c]	−
2	**1e** (R = Ph)	rt	20	77
3	**1e** (R = Ph)	−20	7	82
4	**1c** (R = Me)	rt	5	95
5	**1g** (R = CH_2OBn)	rt	3	97

[a] Reaction conditions: see Table 2. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] Yield 72%, 61% ee.

corresponding homoallylic amines in good yields and excellent ee (entries 5−9). The diastereoselectivities showed the same trend as that for **1b**,**c**: the (*E*)-olefins gave the corresponding anti homoallylic amines as major diastereomers, and the (*Z*)-olefins afforded the corresponding syn isomers. Moreover, compound **1e** had to be rearranged at −20 °C to suppress the formation of a byproduct (see Table 3), which resulted in slightly better diastereoselectivity than at room temperature (entries 6 and 7).

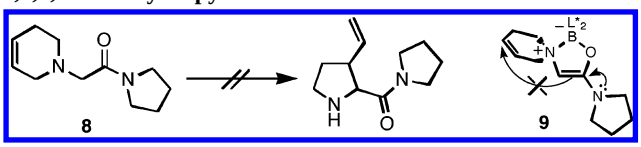
Although the asymmetric rearrangement of the (*E*)-olefin **1h** provided essentially one diastereomer in 99% ee and 52% yield

SCHEME 3. Asymmetric Rearrangement of 1l[a]



[a] For reaction conditions, see Table 1, entry 15.

SCHEME 4 Attempt to Rearrange the 1,2,5,6-Tetrahydropyridine 8[a]



[a] For reaction conditions, see Table 1, entry 15.

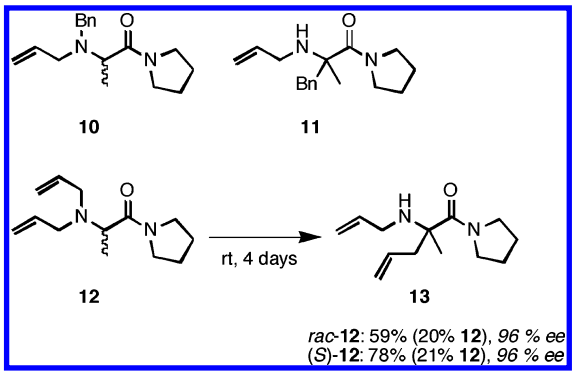
(entry 10), the isomeric (*Z*)-olefin **1i** failed to give the corresponding homoallylic amine, and instead, compound **7i**, the product of a [1,2]-sigmatropic rearrangement, was formed in 72% yield and 61% ee (entry 11 and Table 3, entry 1). Attempts to suppress the [1,2]-pathway by performing the reaction at −20 °C did not affect the outcome.[20] Finally, rearrangement of amines **1j**,**k** afforded the homoallylic amines **2j**,**k** in 99% and 96% ee, respectively (Table 2, entries 12 and 13).

To further extend the scope of the asymmetric rearrangement, (*Z*)-olefin **1l** containing a dimethylamide moiety was prepared. Subjecting this material to the optimized rearrangement conditions furnished a mixture of **2l** (62%), starting material (3%), and benzylic [1,2]-shift product **7l** (17%) (Scheme 3). As expected, the syn diastereomer was the major isomer under these conditions (anti/syn 28:72 for the crude product). After purification, an anti/syn ratio of 26:74 with at least 97% ee for the syn diastereomer was obtained.

In the rearrangement of (*Z*)-olefins **1c**,**e**,**g** minor amounts of the corresponding [1,2]-products could be detected, although the major products in all cases were derived from the [2,3]-rearrangement (Table 3, entries 2−5).[21] With **1e**, the [1,2]-rearrangement became a concern when the reaction was performed at room temperature (entry 2), but by lowering the reaction temperature to −20 °C, the [2,3]-sigmatropic rearrangement prevailed (entry 3). The (*E*)-olefins **1b**,**d**,**f**,**h** gave insignificant amounts of the corresponding [1,2]-rearranged products.

The rearrangement conditions were also attempted on the N-substituted 1,2,5,6-tetrahydropyridine **8**, which would give an efficient entry to substituted pyrrolidines (Scheme 4).[11,22] Unfortunately, no product could be detected and only the starting material and ligand **3a** were recovered. This can be rationalized by examining structure **9**, the deprotonated complex between **8** and **4a**. [2,3]-Sigmatropic rearrangement of **9** would impose a considerable amount of strain that effectively prevents the desired bond formation.

SCHEME 5. Attempted Asymmetric Rearrangement of 10 and 12[a]



[a] For reaction conditions, see Table 1, entry 15.

By introduction of a substituent at the α-carbon of the rearrangement substrate, homoallylic amines with a quaternary stereogenic center should be obtained. Initial attempts to realize this focused on *rac*- and (*S*)-*N*-allyl-*N*-benzyl alanine derivatives **10**. However, subjecting **10** to the standard rearrangement conditions gave only **11**, the product of a benzylic [1,2]-shift, and recovered **10** (Scheme 5). Instead, treatment of diallyl derivatives *rac*- and (*S*)-**12** under the optimized rearrangement conditions provided the α-allyl methyl alanines **13** in 59% and 78% yields and excellent enantioselectivities, respectively. It should be noted that rearrangement of the allyl group via either a [1,2]- or a [2,3]-rearrangement would, in this case, provide identical products.

Reaction of (*E*)-**1** can give complexes **A** and **A′**, which, when subjected to base, would afford **B** and **B′**, respectively (Scheme 6). An equilibration between **B** and **B′** can be envisioned, possibly assisted by Br^- or a base, and similar processes have been suggested previously.[23] As a result, the stereochemical outcome will be determined by the energy difference between transition states **C** and **C′**. In **C′**, an *N*-Ts moiety efficiently blocks the *si*-face of the enolate and thus interferes with the rearrangement, and no such interactions are present in **C**. Thus, the rearrangement will be channeled through transition state **C** affording (2*R*,3*R*)-**2**, which is in concord with the experimental findings.

In this model, the absolute configuration at C2′ is established via *re*- or *si*-face selectivity in the **C**/**C′** transition states, whereas the C2′/C3 relative stereochemistry is generated by the exo/endo orientation of the allyl moiety (Scheme 7). The rearrangement of (*E*)-olefins afforded the anti products as the major diastereomers, and consequently, the reaction proceeds via the *exo*-**C** transition state. In *exo*-**C**, the allyl moiety experiences less steric interactions compared to *endo*-**C**. The increased steric bulk of the R substituent enhances the diastereoselectivity, as both the R substituent and the allylic C2 carbon are oriented away from the bulky interior of the oxazaborocycle.

The rearrangements of the (*Z*)-olefins afforded lower and opposite diastereoselectivities than the corresponding (*E*)-olefins.

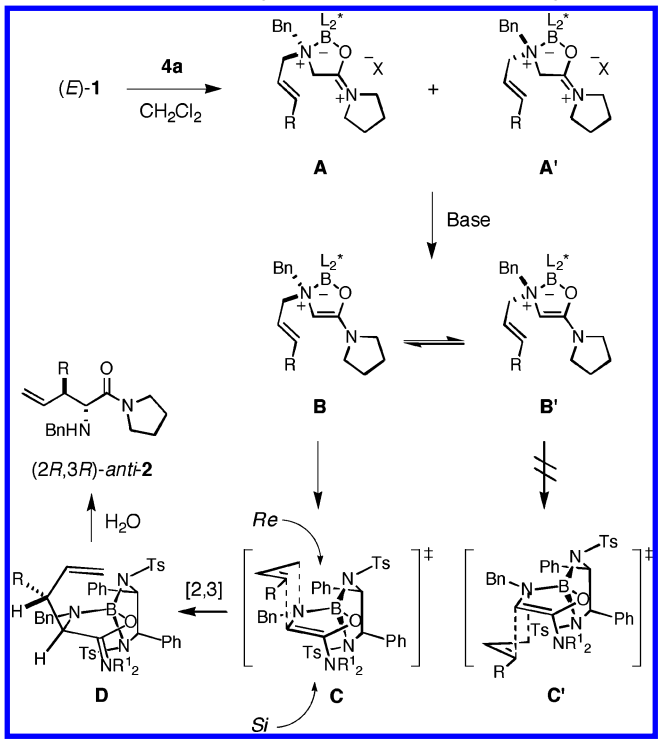
(20) (a) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 1450−1457. (b) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 1436−1449.

(21) The structures of [1,2]-rearranged **1c**,**e**,**g** were confirmed by H,H-COSY.

(22) (a) Burns, B.; Coates, B.; Neeson, S. J.; Stevenson, P. J. *Tetrahedron Lett.* **1990**, *31*, 4351−4354. (b) Sweeney, J. B.; Tavassoli, A.; Carter, N. B.; Hayes, J. F. *Tetrahedron* **2002**, *58*, 10113−10126. (c) Roberts, E.; Sancon, J. P.; Sweeney, J. B.; Workman, J. A. *Org. Lett.* **2003**, *5*, 4775−4777. (d) Roberts, E.; Sancon, J.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075−2078.

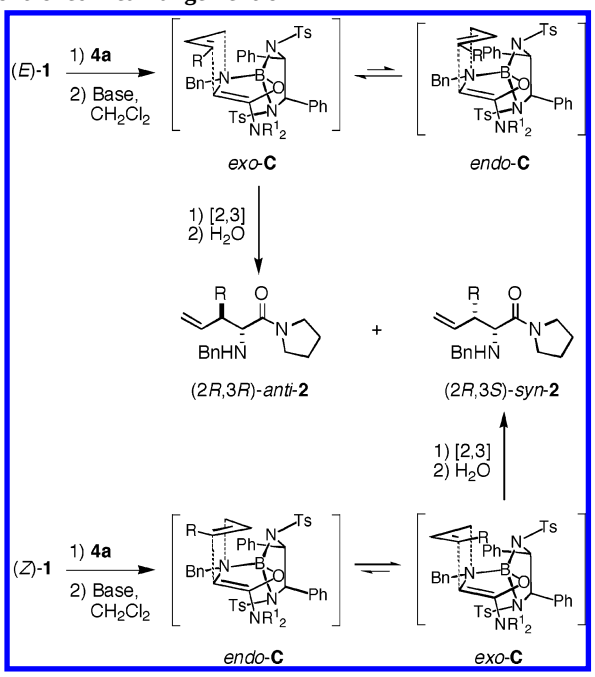
(23) Vedejs, E.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3028−3034. Equilibration before deprotonation and rearrangement can also be envisioned.

SCHEME 6. Kinetically Controlled Stereoselectivity[a]



[a] The charges are omitted in **C** and **C′** for clarity.

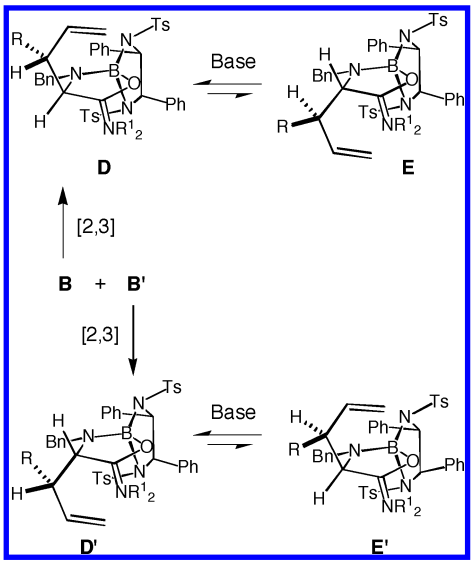
SCHEME 7. Proposed Transition States in the Kinetically Controlled Rearrangement of 1[a]



[a] The charges are omitted for clarity.

This observation can be explained by the fact that both the exo and endo transition states experience unfavorable steric interactions (Scheme 7). In the exo transition state, unfavorable steric interactions between the R substituent and the bulky interior of the oxazaborocycle arise, whereas the endo transition state is destabilized by interaction of the allylic C2 carbon with the interior of the oxazaborocycle. There is a slight preference for the exo transition state, however, though this seems to decrease when the R moiety becomes larger. With **1i** (R = $SiMe_2Ph$), severe steric interactions in both the exo and the endo transition result in a preferential reaction through a benzylic [1,2]-rearrangement (see Table 3).

SCHEME 8. Thermodynamically Controlled Reaction Pathway[a]



[a] Only rearrangement from the exo transition state considered, and the charges are omitted for clarity. For structures B and B′, see Scheme 6.

The stereochemical outcome can also be rationalized by diastereoselective complexation of Lewis acid **4a** to **1**, generating complex **A**. However, this kinetically controlled scenario appears less likely, as the benzyl and allyl groups are sterically and electronically relatively similar.

Alternatively, the stereoselectivities observed in the rearrangements could be under thermodynamic control. In this case, the focus would be on the rearranged complexes **D** and **D′** (Scheme 8). The basic conditions applied in the rearrangement can lead to deprotonation of **D** and **D′**, thus establishing equilibriums between **D** and **E** and between **D′** and **E′**, respectively. Because of unfavorable steric interactions with the *N*-Ts moiety, complexes **D′** and **E** will be destabilized compared to **D** and **E′**. Thus, upon acidic hydrolysis, complex **D** will give the observed major product (2*R*,3*R*)-*anti*-**2**, whereas the thermodynamically less stable complex **E** will provide the minor product (2*S*,3*R*)-*syn*-**2**. Likewise, complex **E′** gives (2*R*,3*S*)-*syn*-**2** and **D′** yields minor product (2*S*,3*S*)-*anti*-**2**. Although this rationale concerns rearrangement of **B** and **B′** via an exo transition state, the analogous event via an endo transition state will merely give the opposite product outcome (**D** will instead provide (2*R*,3*S*)-*syn*-**2**, whereas **E′** will give (2*R*,3*R*)-*anti*-**2**, i.e., the experimentally observed products). In this scenario, the absolute configuration at C2′ is established under thermodynamic control during a base-induced equilibrium. The C2′/C3 relative stereochemistry is established by the relative rate of formation of complexes **D**/**D′** and the exo/endo preference in the transition states.

To investigate this, DFT calculations were performed on complexes **D** (R = H, same as **E′**) and **D′** (R = H, same as **E**).[24] These calculations established that complex **D** (R = H) is about 10 kcal/mol more stable than **D′** (R = H), which is in

(24) For computational details, see ref 14.

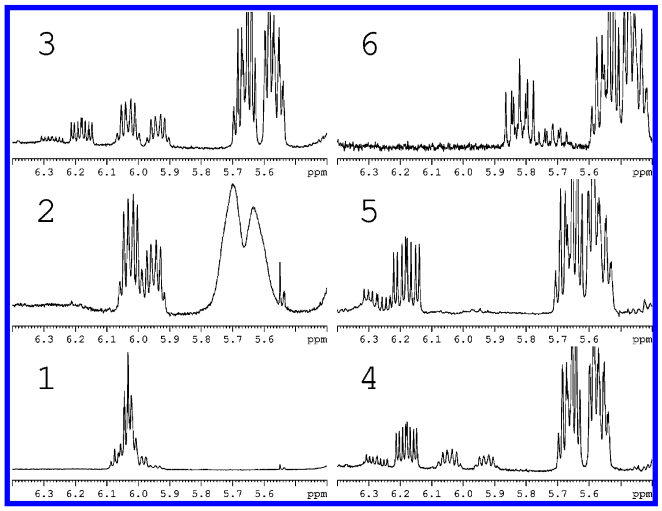


FIGURE 2. ^{1}H NMR spectroscopic investigation of the rearrangement (δ 5.4−6.4 ppm). (1) Complex(es) formed by mixing **1b** (1 equiv) and chiral Lewis acid **4a** (2 equiv). (2) After addition of Et_3N (>2 equiv). (3) After 90 min. (4) After 2 h. (5) After 5−6 h. (6) After acidic hydrolysis and workup.

agreement with the observed reaction outcome. However, a deuterium exchange experiment conducted on complex **6** (Et_3N, D_2O, CH_2Cl_2) resulted in no deuterium incorporation, and consequently, the kinetic process seems more likely.

With the objective to clarify the mechanistic details of the rearrangement, an NMR spectroscopic investigation of the complex formed between **4a** and **1b** along with the formation of the anticipated deprotonated and rearranged complexes **B**/**B′** and *exo*-**D**/*endo*-**D**, respectively, was initiated (Figure 2). Thus, the complex between **4a** and **1b** was formed as previously described and monitored by ^{1}H and ^{11}B NMR spectroscopy. By the upfield change in the chemical shift of the signals from the diastereotopic *N*-allyl and *N*-benzyl protons of **1b**, it appeared that **1b** was converted into complexes **A** and/or **A′**. From the ^{1}H NMR spectroscopic data, it was difficult to establish whether a mixture of the complexes formed or whether an equilibrium between them existed (Figure 2, NMR 1). ^{11}B NMR revealed a broad singlet at δ 10.4 ppm and two broader signals at 23.5 and 27.3 ppm, respectively. The upfield boron signal most likely arose from the complexes **A**/**A′**, and the latter two probably originated from residual chiral Lewis acid. To that solution was added >2 equiv of Et_3N, and the ^{1}H NMR spectrum was instantly recorded (NMR 2). Two sets of signals at approximately δ 6.0 ppm, the vinylic protons in **B** and **B′**, had emerged along with a broad signal at δ 5.6 ppm attributed to starting material **1b**. How **1b** formed is unclear, but the relative integral stayed constant during the experiment (NMR 3−6). The signals corresponding to **B** and **B′** had a 2:1 ratio throughout the NMR experiment and were slowly diminishing relative to the other signals and disappeared within 5−6 h. In the ^{11}B NMR spectrum, the signal at δ 10.4 ppm had endured, but now only one broad signal appeared at δ 22.8 ppm. While the signals in the ^{1}H NMR spectrum corresponding to complexes **B**/**B′** diminished, two new signals at δ 6.2 and δ 6.3 ppm appeared and were interpreted as allylic C2 protons of the rearranged complexes **D** and **E′**, respectively (NMR 3). The ratio between the two signals was 4:1 and remained constant during the experiment (NMR 3−5). During this time, the signal at δ 10.4 ppm in the ^{11}B NMR spectrum also diminished and was replaced by a signal at approximately δ 9 ppm, probably arising from the rearranged complexes **D** and **E′**. This signal is in agreement with the ^{11}B NMR spectrum of complex **6**. Moreover, by inspection of the ^{1}H integrals, it could be established that the relative amount between the complexes and amine **1b** remained constant during the acquisitions of NMR 2−6.

Our rationalization of the data from the NMR spectroscopic investigation is as follows. Complexes **B** and **B′** existed in a slow equilibrium in a 2:1 relationship (NMR time scale, NMR 2−4).[23] Nevertheless, in the kinetic scenario, only complex **B** rearranged, either via the *exo*- or *endo*-**C** transition state, to provide an 80:20 diastereomeric ratio of rearranged complexes **D** and **E′**. After the rearrangement was complete (NMR 5), acidic hydrolysis and workup provided (2*R*,3*R*)-**2b**/(2*R*,3*S*)-**2b** in an 80:20 diastereoselectivity and >97 and 82% ee, respectively, together with recovered starting material (NMR 6). Consequently, the NMR investigation suggests that a kinetic pathway such as the one described may well be responsible for the stereochemical outcome.

Conclusions

The first asymmetric [2,3]-sigmatropic rearrangement of achiral allylic amines has been realized by employing the chiral Lewis acid **4a**. The scope of the rearrangement was demonstrated on several amines, affording the corresponding homoallylic secondary amines **2** in excellent ee's and good diastereoselectivities. A study of the diastereoselectivity was provided by four different (*E*)/(*Z*)-olefinic pairs, suggesting an exo preference in the transition state of the rearrangement. The obtained stereoselectivities were rationalized by invoking either a kinetic or a thermodynamic pathway. The kinetic pathway was favored in light of the results from a D_2O-quenching experiment of the isolated rearranged complex **6** and a NMR spectroscopic investigation of the process.

Experimental Section

Representative Experimental Description for the Asymmetric [2,3]-Sigmatropic Rearrangement of Amines 1. (2*R*,3*R*)-2-(Benzylamino)-3-((benzyloxy)methyl)-1-(pyrrolidin-1-yl)pent-4-en-1-one (*anti*-2d). To a solution of the ligand **3a** (115 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (0.22 mL, 1 M in CH_2Cl_2), and the resultant mixture was stirred for 1.5 h at room temperature. The solvent was removed in vacuo, and fresh CH_2Cl_2 (2 × 2 mL) was added and removed in vacuo to provide an off-white solid.[25] To the solid was transferred **1f** (42 mg, 0.11 mmol) in CH_2Cl_2 (2 mL), and the resultant solution was stirred for 1 h before Et_3N (80 μL, 0.56 mmol) was added. After 20 h, the reaction mixture was treated with conc. HCl/MeOH (1:5, 2 mL) overnight at room temperature.[26] To the cooled solution was added 2 M NaOH (1 mL) and saturated $NaHCO_3$ (5 mL), and the water phases were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (K_2CO_3) and concentrated, and the residue was triturated with Et_2O (3 × 1 mL) to provide the ligand **3a** (100 mg, 87%) as a solid. The Etheral triturate was concentrated and purified by chromatography (acetone/pentane 0:1→1:2 + 0.3% ^{i}PrNH$_2$) to provide **2f** (29.2 mg, 70%) as a diastereomeric mixture (anti/syn 88:12) and the remaining ligand **3a** (14.5 mg, 13%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.31−7.18 (m, 10H), 5.83 (ddd, J = 17.4, 10.5, 8.1 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.07 (d, J = 17.4 Hz, 1H), 4.41 (s, 2H), 3.83 (d, J = 13.3 Hz, 1H), 3.67 (dd, J =

(25) This procedure was necessary to remove all HBr from the reaction vessel.

(26) The reaction time could be shortened to 1−2 h by heating at 60 °C.

8.9, 7.8 Hz, 1H), 3.61 (d, $J = 4.8$ Hz, 1H), 3.52 (d, $J = 13.3$ Hz, 1H), 3.52 (m, 2H), 3.40 (m, 2H), 3.16 (m, 1H), 2.55 (m, 1H), 2.22 (bs, 1H), 1.81 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 172.4, 140.4, 138.4, 135.2, 128.32, 128.25, 128.2, 127.48, 127.46, 126.8, 117.5, 73.2, 71.0, 58.6, 52.3, 46.6, 45.9, 45.6, 26.1, 24.1. IR (neat) 3323, 3030, 2873, 1637, 1452, 1101 cm^{-1}. HRMS (FAB+) calcd for $C_{24}H_{31}N_2O_2$ $[M + H]^+$: 379.2386. Found: 379.2387. $[\alpha]_D^{20}$ +15.4 ($c = 0.49$, CH_2Cl_2).

Acknowledgment. This work was supported financially by the Swedish Research Council and the Knut and Alice Wallenberg foundation. We are grateful to Dr. T. Privalov for ab initio calculations and to Dr. Andreas Fischer for X-ray structure determination.

Supporting Information Available: Experimental procedures and spectral data characterizations of all new compounds. X-ray data of compound **6** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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