JOC Article

Lewis Acid Mediated [2,3]-Sigmatropic Rearrangement of Allylic α-Amino Amides

Jan Blid,[†] Peter Brandt,[‡] and Peter Somfai*,[†]

Organic Chemistry, KTH Chemistry, Royal Institute of Technology, SE-100 44 Stockholm, Sweden, and Department of Structural Chemistry, Biovitrum AB, SE-112 76 Stockholm, Sweden

somfai@kth.se

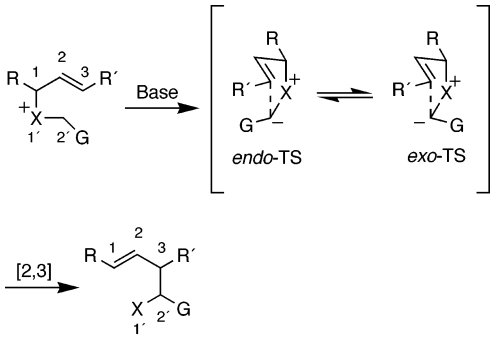
Received November 4, 2003

Boron trifluoride and BBr_3 mediated [2,3]-sigmatropic rearrangements of allylic α-amino amides have been developed affording secondary amines in good yields. (*E*)-Crotyl and (*E*)-cinnamyl α-amino amides **2b** and **2c** exhibit excellent *syn*-diastereoselectivity upon rearrangement with either Lewis acid. The allylic amine **2a** forms upon treatment with BF_3 or BBr_3 a five-membered heterocylic complex in which a single halide anion has been displaced by the carbonyl oxygen atom. The structures of the Lewis acid−amine complexes were elucidated using NMR spectroscopy. A plausible reaction mechanism, based on DFT calculations, is presented. Thus, BF_3- or BBr_3-complexed allylic amines **2** are shown to preferentially proceed, after deprotonation, via an *endo* transition state.

Introduction

Carbon−carbon bond-forming reactions are of central importance in organic chemistry. Consequently, much effort has been expended in this area, and of particular interest are transformations that introduce the new bond in high regio- and stereoselectivity. Although a plethora of these reactions have been successfully developed, the pursuit of stereocontrolled C−C bond-forming reactions is still a challenging goal. In this respect, ylidic [2,3]-sigmatropic rearrangement reactions are useful tools for forming new C−C bonds (Scheme 1).[1] Several ylidic precursors such as amines,[2] sulfides,[3] ethers,[4] selenides,[5] and halogens[6] have been investigated, establishing this rearrangement as a powerful and diverse transformation.

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



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

The rearrangement is believed to proceed via a concerted five-membered cyclic transition state.[7,8] 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] An attractive feature of the [2,3]-sigmatropic rearrangement is that it creates a new C−C bond adjacent to both the heteroatom and the anion-stabilizing group. Also, the olefin moiety provides possibilities for further functionalization, and the efficacy of the reaction has been demonstrated by application in a number of natural product syntheses.[9] One drawback inherent in the [2,3]-sigmatropic rearrangement of ylides

* Corresponding author. Phone: (+46)-8-790 6960. Fax: (+46)-8-791 2333.
† Royal Institute of Technology.
‡ Department of Structural Chemistry, Biovitrum AB.

(1) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913−974.

(2) Some recent examples: (a) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31−33. (b) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236−238. (c) Smith, R. S.; Bentley, P. D. *Tetrahedron Lett.* **2002**, *43*, 899−902. (d) Sweeney, J. B.; Tavassoli, A.; Carter, N. B.; Hayes, J. F. *Tetrahedron* **2002**, *58*, 10113−10126.

(3) Selected references: (a) Blackburn, G. M.; Ollis, W. D.; Plackett, J. D.; Smith, C.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1968**, 186−188. (b) Baldwin, J. E.; Hackler, R. E.; Kelly, D. P. *J. Chem. Soc., Chem. Commun.* **1968**, 537−538. (c) Chappie, T. A.; Weekley, R. M.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 6523−6526. (d) Gulea, M.; Marchand, P.; Masson, G.; Saquet, M.; Collignon, N. *Synthesis* **1999**, 1635−1639. (e) Aggarwal, V. K.; Ferrara, M.; Hainz, R.; Spey, S. E. *Tetrahedron Lett.* **1999**, *40*, 8923−8927.

(4) (a) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917−1925. (b) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060−6062. (c) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062−6063. (d) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50−61.

(5) (a) Gassman, P. G.; Miura, T.; Mossman, A. *J. Org. Chem.* **1982**, *47*, 954−959. (b) Nishibayashi, Y.; Ohe, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1245−1264. (c) Kurose, N.; Takahashi, T.; Koizumi, T. *J. Org. Chem.* **1997**, *62*, 4562−4563.

(6) (a) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094−5102. (b) Simonneaux, G.; Galardon, E.; Paul-Roth, C.; Gulea, M.; Masson, S. *J. Organomet. Chem.* **2001**, *617−618*, 360−363.

(7) (a) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1971**, 1494−1495. (b) Rautenstrauch, V. *Helv. Chim. Acta* **1972**, *55*, 2233−2240.

(8) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1953−1962.

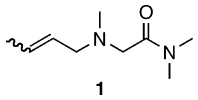
10.1021/jo035618g CCC: $27.50
Published on Web 03/27/2004

is that the heteroatom moiety in the resultant product is fully substituted rendering further derivatization of this functionality problematic.

We have recently demonstrated that activation of tertiary allylic amino amides with BBr_3 followed by deprotonation with a strong base promote the [2,3]-sigmatropic rearrangement.[10] The resultant secondary amines are formed in good yields and with high diastereoselectivity, establishing the reaction as an efficient approach to α-amino acid derivatives.[11] Herein is described the full details of that investigation. In addition, computational and NMR spectroscopic investigations of the rearrangement have been performed, the details of which will be presented.

Computational Methods

Model System. The *N*-benzyl group of **2a** was replaced by a methyl group to avoid the requirement of conformational sampling and the pyrrolidine in the amide moiety was replaced by a dimethylamine affording model compound **1**.



1

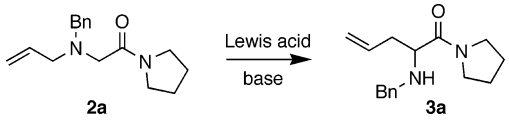
Density Functional Theory Calculations. All geometric optimizations together with final gas-phase energy determinations were performed using the B3LYP hybrid density functional.[12] Geometric optimizations and vibrational analyses were performed with the Jaguar program using the LACVP basis set keyword.[13] LACVP refers to the use of the double-ζ quality LANL2DZ basis set for Br and the 6-31G basis set for other atoms.[14] LANL2DZ implies the use of effective core potentials for 28 electrons of bromine and the use of a (3s,3p) primitive basis contracted to [3s,2p]. Transition state searches were performed using the quadratic synchronous transit (QST) method. Final energies were calculated in Jaguar using the 6-311+G** basis set.

Solvation free energies were calculated with the polarized continuum model (PCM/HF/6-31+G*)[15] in the Gaussian 98 program package.[16]

Results and Discussion

Screening of Brønsted Bases. Previous investigations have shown that Lewis acid mediated [2,3]-sigmatropic rearrangements of α-amino esters proceed with low conversion.[17] Since enolates derived from amides tend to be more reactive then ester enolates, compound **2a** was selected as model substrate together with $BF_3{\cdot}OEt_2$ as a Lewis acid for initial screening experiments (Scheme 2).

SCHEME 2. Lewis Acid Mediated [2,3]-Sigmatropic Rearrangement of 2a



2a **3a**

TABLE 1. BF_3-Assisted Rearrangement of 2a[a]

entry	$BF_3{\cdot}OEt_2$ (equiv)	base/(equiv)	*T* (°C)/*t* (h)	**3a**[b] (%)
1	1.1	LDA/3.0	rt/16	NR[c]
2	3.0	KHMDS/3.0	−20/23	4 (42)
3	1.2	KHMDS/1.2[d]	−20/20	12 (63)
4[e]	1.2	*i*-Pr_2NEt/1.2	reflux/13 h	57 (15)

[a] Reaction conditions: to **2a** in THF were added $BF_3{\cdot}OEt_2$ and base. [b] Yields determined by HPLC. Yield of recovered starting material in parentheses. [c] NR = no reaction. [d] 1.2 equiv of 18-crown-6 was added. [e] PhMe used as solvent.

Treating **2a** with $BF_3{\cdot}OEt_2$ followed by addition of various bases either provided **3a** in low yields or did not effect the desired rearrangement (Table 1, entries 1−3). The best yield was achieved when using equimolar amounts of $BF_3{\cdot}OEt_2$ and KHMDS in the presence of 18-crown-6, affording a mere 12% of **3a** (entry 3). Attempts to improve the outcome by varying the reaction temperature and amount of reagents met with no success. Interestingly, when employing the weaker base *i*-Pr_2NEt a smooth rearrangement took place at elevated temperatures, affording **3a** in 57% yield (entry 4). Encouraged by this result, it was decided to investigate whether stronger neutral bases could promote the rearrangement at lower temperatures. Hence, the Schwesinger phosphazene bases **4**−**6** were chosen, due to their commercial availability and ease of handling (Figure 1).[18]

The complex formed by mixing **2a** and $BF_3{\cdot}OEt_2$ was treated with phosphazene bases **4**−**6**. From the results a clear trend could be discerned: using stronger bases increased the yield of **3a** (Table 2). Phosphazene bases **4** and **5** gave at −20 °C similar yields of **3a** as KHMDS (entries 1 and 3 vs Table 1, entry 3), while higher yields were obtained at room temperature (entries 2 and 4). The stronger phosphazene base **6** gave a substantial increased yield of **3a**: 36% at −20 °C and 42% at room temperature (entries 5 and 6). Although these results did not produce as high yields as with using *i*-Pr_2NEt, the rearrangement could be run at lower temperatures.

(9) (a) Blackburn, G. M.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1969**, 99. (b) Kaiser, G. V.; Ashbrook, C. W.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 2342−2344. (c) Trost, B. M.; Conway, P.; Stanton, J. *J. Chem. Soc., Chem. Commun.* **1971**, 1639−1640. (d) Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 7573−7574. (e) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453−5461. (f) Vedejs, E.; Reid, J. G.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4351−4357.

(10) Blid, J.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 3159−3162.

(11) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(12) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(13) Jaguar 4.0, Schrödinger, Inc., Portland, OR, 1991−2000.

(14) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 285. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(15) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(17) (a) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2817−2821. (b) Murata, Y.; Nakai, K. *Chem. Lett.* **1990**, 2069−2072.

(18) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G. Z.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann./Recueil* **1996**, 1055−1081.

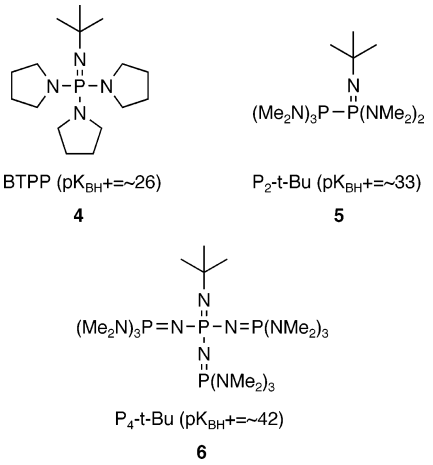


FIGURE 1. Schwesinger phosphazene bases **4**−**6**.

TABLE 2. Rearrangement of 2a To Give 3a Mediated by BF_3·OEt_2 and Phosphazene Bases 4−6[a]

entry	base	*T* (°C)	**3a**[b] (%)
1	**4**	−20	11 (62)
2	**4**	rt	24 (61)
3	**5**	−20	12 (78)
4	**5**	rt	31 (68)
5	**6**	−20	36 (64)
6	**6**	rt	42 (50)

[a] Reaction conditions: to **2a** (1.0 equiv) in PhMe at −78 °C were added BF_3·OEt_2 (1.2 equiv) and base (1.2 equiv), and the resultant mixture was stirred overnight (18−20 h). [b] Yield of recovered starting material in parentheses.

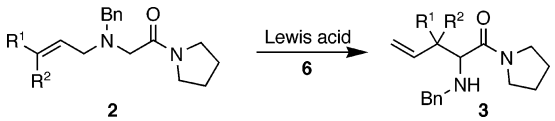
TABLE 3. Rearrangement of 2a To Give 3a Mediated by Various Lewis Acids and 6[a]

entry	LA/(equiv)	*T* (°C)	**3a**[b] (%)
1	BF_3/1.2	−20	36 (64)
2	BCl_3/1.2	−20	46 (40)
3	BBr_3/1.2	−20	66 (22)
4	Bu_2BOTf/1.2	rt	0 (93)
5	$InCl_3$/1.1	rt	14 (63)
6	$ZnCl_2$/1.0	rt	23 (68)
7	No LA	rt	0 (91)

[a] Reaction conditions: to **2a** (1.0 equiv) in PhMe at −78 °C were added Lewis acid and **6** (1.2 equiv). Stirred overnight (16−20 h) at −20 °C or rt. [b] Yield of recovered starting material in parentheses.

Screening of Lewis Acids. With useful conditions for the rearrangement at hand, a survey of various Lewis acids was planned, and initial focus was directed toward those containing boron. When applying BCl_3 or BBr_3, which are both considered to be stronger Lewis acids than BF_3,[19,20] **3a** was obtained in 46% and 66% yield, respectively (Table 3, entries 2 and 3); however, when Bu_2BOTf was used to promote the rearrangement, **2a** was recovered unaffected (entry 4). It was also found that $InCl_3$ and $ZnCl_2$ promoted the rearrangement but afforded **3a** in only low yields (entries 5 and 6), while other Lewis acids, e.g., CuCl, $CuCl_2$, $TiCl_4$, $Yb(OTf)_3$, $FeCl_3$, $ZrCl_2Cp_2$, and $ScCl_3$ failed to promote the process. A control experiment was also conducted. Treatment of **2a** with **6** in the absence of a Lewis acid did not furnish the rearrangement (entry 7). It was also noted that when the complex formed by mixing BBr_3 and **2a** was reacted with weaker nonionic bases, such as **4**, **5**, or Et_3N, compound **3a** was formed in yields comparable that obtained when using phosphazene **6**. On the other hand, LDA did not promote the BBr_3-mediated rearrangement as efficiently and afforded **3a** in only 31% yield (53% recovered starting material).

TABLE 4. Rearrangements of Amines 2b−e[a]

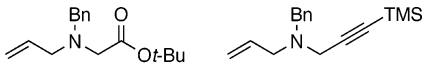


entry	amine	R^1	R^2	Lewis acid	**3**[b] (%)	syn/anti[c]
1	**2b**	Me	H	BBr_3	**b** 71 (20)	>20:1
2	**2c**	Ph	H	BBr_3	**c** 62 (32)	11:1
3	**2d**	H	Me	BBr_3	**d** 56 (33)	6:5
4	**2e**	Me	Me	BBr_3	**e** 60 (31)	
5	**2b**	Me	H	BF_3·OEt_2	**b** 14 (48)	>20:1

[a] Reaction conditions: to the amine (1.0 equiv) in PhMe at −78 °C were added Lewis acid (1.1 equiv) and **6** (1.0 equiv), and the resultant mixture was stirred overnight (18−20 h) at −20 °C. [b] Yield of recovered starting material in parentheses. [c] Ratio determined by ^{1}H NMR.

Scope and Stereoselectivity. To investigate the scope and stereoselectivity of the rearrangement amines **2b**−**e** were prepared. Gratifyingly, di- and trisubstituted olefins **2b**−**e** showed similar reactivity as the allyl derivative **2a** (Table 4). *E*-Olefins **2b** and **2c** rearranged with high diastereoselectivity, affording *syn*-**3b** in 71% yield and >20:1 ds, and *syn*-**3c** in 62% yield and 11:1 ds, respectively (entries 1 and 2). However, *Z*-olefin **2d** afforded **3d** with poor syn:anti selectivity (entry 3). Boron trifluoride also furnished *syn*-**3b** with high diastereoselectivity, albeit in low yield (entry 5).

The anion-stabilizing group can influence the stereochemical outcome of [2,3]-sigmatropic rearrangements.[8,21] To investigate if this was also the case for the title reaction and hopefully improve diastereoselectivity in the rearrangements of Z-olefins corresponding to **2d**, ester and propargyl substrates **7** and **8** were prepared. When subjected to BBr_3 and base **6** neither of the two substrates provided the corresponding products. Ester **7** was probably transformed to the corresponding acid under the reaction conditions since only a small amount of **7** could be recovered, while starting material was retrieved exclusively when amine **8** was subjected to identical conditions.



Density Functional Calculations. Understanding the reaction mechanism could provide information regarding some of the experimental observations discussed above.[22] Of particular interest is the diastereoselectivity of the reaction and the role of the Lewis acid. Understanding this could facilitate the design of chiral auxil-

(19) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: New York, 1978.

(20) Ishihara, K. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 89−133.

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

SCHEME 3. Anionic Reaction Paths for the Lewis Acid Mediated [2,3]-Sigmatropic Rearrangement of *E*-1 (X = F or Br)

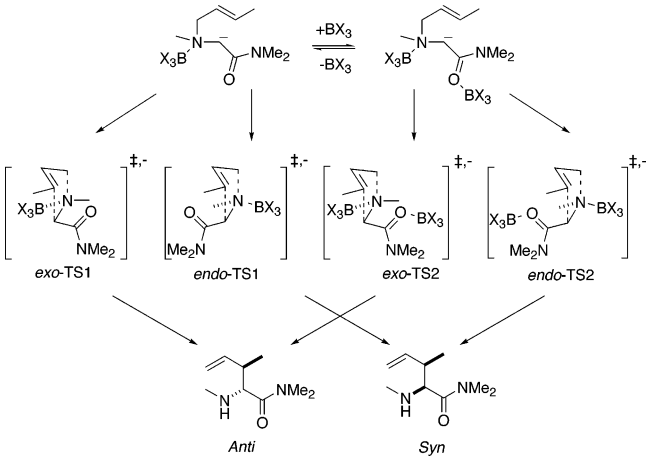


TABLE 5. Activation Free Energies (kcal mol^{-1}) for the Anionic Mechanism[a]

LA	TS	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$ [b]
BF_3	*exo*-**TS1**	18.7	
	endo-**TS1**	19.9	1.2
	exo-**TS2**	19.6	
	endo-**TS2**	19.4	−0.2
BBr_3	*exo*-**TS1**	25.5	
	endo-**TS1**	27.8	2.3

[a] Solvation effect included in the free energy. [b] Calculated diastereoselectivity, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(endo) − $\Delta G^{\ddagger}$(exo).

iaries and also help identify new substrates suitable for the reaction. As part of an initial hypothesis, we investigated the chemistry surrounding the deprotonated, BF_3- or BBr_3-coordinated α-amino amide **1**. Two different coordination modes were investigated as illustrated in Scheme 3, and an inactivated state characterized by a single BX_3 binding to the amide oxygen was also taken into account.

The results given in Table 5 exhibit concordant theoretical activation energies for the BF_3-promoted reaction but the calculated diastereoselectivities are not in accordance with the experimental result. In the case of the BBr_3-promoted reaction, the calculated activation energies are well above the limits suggested by the time of the experimental reaction. Again, the predicted diastereoselectivity is erroneous. The high activation energy in case of BBr_3 appears to be due to a very strong coordination of this Lewis acid to the amide oxygen.

At this point, alternative reaction mechanisms had to be explored. One possible alternative would be a mechanism where the carbonyl oxygen atom displaces one of the halides from the Lewis acid. It has previously been established that boron Lewis acids, such as $ArBF_2$ and BF_3, form cyclic complexes with *N*,*N*-dialkylamino acids by displacing a fluoride anion.[23] These complexes can

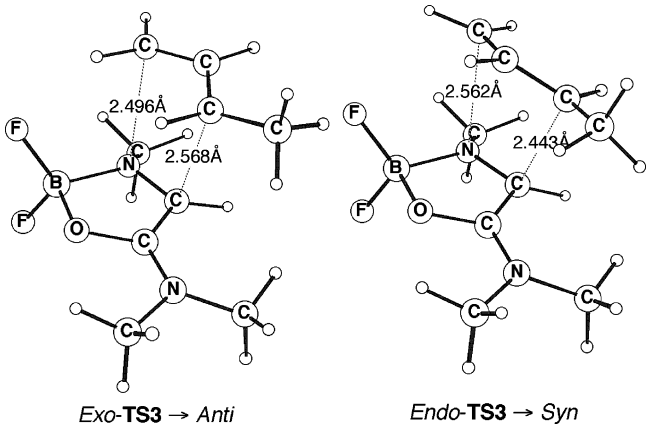


FIGURE 2. Diastereomeric transition states for the neutral BF_2^+-mediated [2,3]-sigmatropic rearrangement of *E*-**1**.

TABLE 6. Activation Free Energies (kcal mol^{-1}) for the Neutral Mechanism (Figure 2)[a]

LA	substrate	TS	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$ [b]	$\Delta\Delta G^{\ddagger}$ (exp)[c]
BF_2^+	*E*-**1**	*exo*-**TS3**	22.3		
	E-**1**	*endo*-**TS3**	21.0	−1.3	<−1.7
BBr_2^+	*E*-**1**	*exo*-**TS3**	17.4		
	E-**1**	*endo*-**TS3**	15.8	−1.6	<−1.5
BBr_2^+	*Z*-**1**	*exo*-**TS3**	17.2		
	Z-**1**	*endo*-**TS3**	17.4	0.2	≈−0.1

[a] Solvation effect included in the free energy. [b] Calculated diastereoselectivity, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(endo) − $\Delta G^{\ddagger}$(exo). [c] Calculated from the experimentally determined diastereomeric ratio.

easily be characterized from their ^{11}B and ^{19}F NMR through the $^{11}B-^{19}F$ splitting pattern and chemical shifts (vide infra).[19,24] It was assumed that similar complexes would be formed between BF_3 or BBr_3 and substrate **2a**.

Initially, we investigated the energetics of the reaction wherein one halide is displaced by the bidentate substrate. Starting with BF_3, the calculations suggest that the displacement is endergonic by 12.4 kcal mol^{-1}. In the case of BBr_3, the reaction is conversely favorable by −13.7 kcal mol^{-1} of free energy. The unfavorable BF_3 mediated reaction could be promoted via addition of an additional 1 equiv of the Lewis acid to account for the liberated fluoride ion. Theoretically, this makes the reaction exergonic by −14.9 kcal mol^{-1}. The analogous reaction with an additional equivalent of BBr_3 predicted a favorable reaction with a free energy of −32.6 kcal mol^{-1}. Thus, the reactions seem likely to exhibit differing chemistry. Whereas the BF_3-mediated process could not enter this rearrangement pathway without consuming an additional equivalent of the Lewis acid, the BBr_3 reaction is likely to be less dependent on an additional equivalent. Figure 2 shows the two diastereomeric transition states possible for the BF_2^+-mediated [2,3]-sigmatropic rearrangement of *E*-**1**. No apparent structural cause for the selectivity is revealed by these structures. However, this type of transition state generates both acceptable rates of the reaction and a correct estimation of the diastereoselectivity as shown in Table 6.

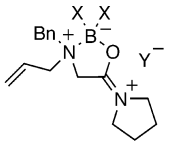
NMR Spectroscopic Investigation of Complexes 9a,b. To determine the structure of the complexes formed

(22) DFT-calculations on related [2,3]-sigmatropic rearrangements: (a) Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421−1423. (b) Mikami, K.; Uchida, T.; Hirano, T.; Wu, Y.-D.; Houk, K. N. *Tetrahedron* **1994**, *50*, 5917−5926. (c) Jursic, B. S. *THEOCHEM* **1995**, *339*, 161−168.

(23) (a) Halstrøm, J.; Nebelin, E.; Pedersen, E. J. *J. Chem. Res.* **1978**, 80−81. (b) Vedejs, E.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3028−3034.

(24) Harris, R. K.; Mann, B. E. *NMR and the Periodic Table*; Academic Press: London, 1978.

by mixing the Lewis acid with the substrate **2a** and to find additional support for the computationally determined reaction pathway, an NMR spectroscopic investigation was undertaken. Consequently, adding 1 equiv of BF_3·OEt_2 to **2a** afforded, according to ^{1}H NMR, approximately a 3:2 mixture of **2a** and the **2a**−BF_2 complex **9a**, and addition of a second equivalent of BF_3·OEt_2 transformed the remaining **2a** into **9a**.



9a; X=F, Y=BF_4
9b; X=Br, Y=Br or BBr_4

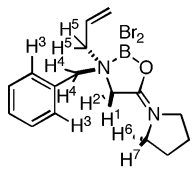
Examining the ^{11}B NMR spectrum of **9a** revealed one triplet at δ 4.9 ppm ($^1J_{B,F}$ = 15 Hz) and one singlet at δ −0.7 ppm.[25] The triplet signal was indicative of a boron atom with two fluorine substituents, and the observed ^{11}B chemical shift was in good agreement with those observed with related compounds.[23] It can be suggested that 1 equiv of BF_3·OEt_2 was required for the complexation to **2a** while the second reacted with the liberated F^- forming BF_4^-, which corresponds to the ^{11}B signal at δ −0.7 ppm ($^1J_{B,F}$ = ∼1 Hz gives apparent singlet).[19] In the ^{19}F NMR spectrum of **9a**, two multiplet signals at δ −85.7 and −88.5 ppm were observed corresponding to the diastereotopic fluorine atoms[26] and a singlet at −88.6 ppm arising from BF_4^-.[24,27]

When BBr_3 and **2a** were mixed in equimolar amounts, ^{1}H NMR spectroscopy revealed that two distinct complexes were formed in a 5:2 ratio. Increasing the relative amount of BBr_3 to 2 and 3 equiv increased the ratio between the two complexes to 5:1 and 8:1, respectively. The appearance of the two complexes on ^{1}H NMR changed on going from 1 to 2 equiv of BBr_3 but was unchanged with a further increase to 3 equiv.

Examining the ^{11}B NMR spectra revealed one major peak at δ 5.7. At 1 equiv of BBr_3 an additional minor signal at δ −24.3 was observed. At 2−3 equiv of BBr_3, the signal at δ −24.3 disappeared and instead a minor peak at δ −11.8 was revealed. Although the ^{11}B chemical shift of 5.7 ppm and the matching appearance of the ^{1}H NMR with that of complex **9a** suggested a similar chelating complex, the structure of **9b** could not be confirmed by ^{1}H and ^{11}B NMR alone. However, the problem was resolved by 2D NOESY spectroscopy (Table 7). NOE enhancement measurements showed that H^1 exhibited NOE interactions with H^3 and H^4 (entries 1 and 2), while negligible interactions (<1%) were observed between H^1 and H^5. The opposite was the case for H^2 (entry 3). The two methylene protons, H_6 and H_7 on the pyrrolidine ring, exhibited opposite NOE interactions toward H_1 and H_2 further supporting the assignment of complex **9b** (entries 4−7). Similar NOE interactions could be found when examining complex **9a**.

Having established the structures of complexes **9a**,**b**, the rearrangement of **2b**−**d** was repeated with 2 equiv of BF_3·OEt_2, and the results are collected in Table 8. For **2b**, these conditions resulted in an increased yield of **3b** without compromising diastereoselectivity (entries 1 and 2). Using identical reaction conditions, **2c** gave a similar yield of 52% and an excellent diastereoselectivity of >30:1 (entry 3). Surprisingly, the (*Z*)-olefin **2d** was unreactive providing a very low yield and diastereoselectivity regardless of the amount of BF_3·OEt_2 employed (entries 4 and 5). Subjecting **2b** and **2d** to 2 equiv of BBr_3 did not significantly influence the yield or diastereoselectivity (entries 6−9).

TABLE 7. NOE Enhancement Measurements of 9b[a]



9b

entry	NOE interaction	NOE enhancement (%)
1	$H^1 \rightarrow H^3$	6
2	$H^1 \rightarrow H^4$	5
3	$H^5 \rightarrow H^2$	6
4	$H^6 \rightarrow H^2$	4
5	$H^6 \rightarrow H^1$	<1
6	$H^7 \rightarrow H^1$	5
7	$H^7 \rightarrow H^2$	<1

[a] Mixing time: 800 ms (T1 = 1.2 s).

TABLE 8. BF_3- and BBr_3-Mediated [2,3]-Sigmatropic Rearrangements of Amines 2b−d[a]

entry	amine	Lewis acid/(equiv)	syn/anti[b]	**3**[c] (%)
1	(*E*)-Me, **2b**	BF_3·OEt_2/1.1	>30:1	14 (48)
2	(*E*)-Me, **2b**	BF_3·OEt_2/2.0	>30:1	55 (22)
3	(*E*)-Ph, **2c**	BF_3·OEt_2/2.0	>30:1[d]	52 (35)
4	(*Z*)-Me, **2d**	BF_3·OEt_2/1.1	3:1	2 (56)
5	(*Z*)-Me, **2d**	BF_3·OEt_2/2.0	2:1	3 (72)
6	(*E*)-Me, **2b**	BBr_3/1.1	>20:1	71 (20)
7	(*E*)-Me, **2b**	BBr_3/2.0	>20:1	78 (10)
8	(*Z*)-Me, **2d**	BBr_3/1.1	6:5	56 (33)
9	(*Z*)-Me, **2d**	BBr_3/2.0	4:3	49 (22)

[a] Reaction conditions: to **2** (1.0 equiv) in PhMe at −78 °C were added Lewis acid and **6** (1.0 equiv), and the resultant mixture was stirred overnight (18−20 h) at −20 °C. [b] Ratio determined by ^{1}H NMR. [c] Yield of recovered starting material in parentheses. [d] Only one diastereomer visible on crude ^{1}H NMR.

Determination of Relative Stereochemistry of *syn*-3b, *anti*-3b, and *syn*-3c. *syn*-**3b**, *anti*-**3b** and *syn*-**3c** were converted into pyrrolidines **10a**, **10b**, and a mixture of **10c** and **11**, respectively, by Hg^{2+}-mediated cyclization followed by reductive demercuration (Scheme 4). The relative stereochemistry of **10a**,**b** and **11** could then be determined by NOE experiments (Figure 3).

Conclusions

The structures of complexes **9a** and **9b** have been confirmed by NMR spectroscopy. While the complex **9b** was readily formed by mixing **2a** with 1 equiv of BBr_3, an additional 1 equiv of BF_3 was needed to account for the displaced fluoride anion upon forming the complex **9a** allowing the reaction to proceed. It has been shown that reaction of amines **2a**−**e** with BBr_3 followed by deprotonation results in a [2,3]-sigmatropic rearrange-

(25) Relative to BF_3·OEt_2 as external standard.
(26) Relative to $CF_3C_6H_5$ as external standard.
(27) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027.

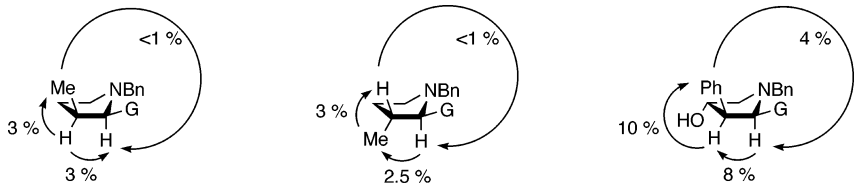
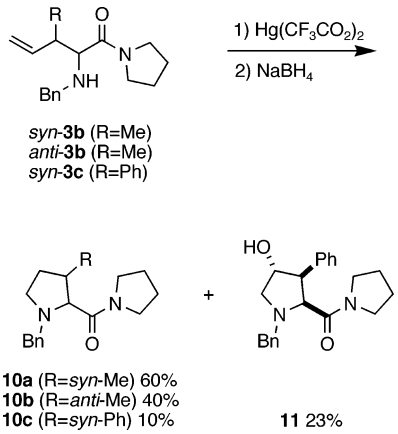


FIGURE 3. NOE enhancement measurements of amines **10a**,**b** and **11**. Mixing times were 700 (T1 = 1.1 s), 600 (T1 = 0.9 s), and 1250 ms (T1 = 1.9 s) for **10a**,**b** and **11**. G = $CON(CH_2CH_2)_2$.

SCHEME 4. Hg^{2+}-Mediated Cyclization of the Secondary Amines *syn*-3b, *anti*-3b, and *syn*-3c



ment affording secondary amines **3** in good yields. (*E*)-Crotyl- and (*E*)-cinnamylamine **2b** and **2c** displayed excellent *syn*-diastereoselectivities in the rearrangement.

DFT calculations on the deprotonated BF_2^+−**1** and BBr_2^+−**1** complexes were in agreement with the experimentally obtained diastereoselectivities, thereby providing a plausible reaction pathway for the BF_3- and BBr_3-mediated [2,3]-sigmatropic rearrangement of allylic α-amino amides.

Experimental Section

Typical Procedure for the Lewis Acid [2,3]-Sigmatropic Rearrangement of Allylic Amines 2. (2*R,3*S**)-1-(2-Benzylamino-3-methyl-1-oxo-4-pentenyl)pyrrolidine (*syn*-3b).** To a stirred solution of **2b** (35 mg, 0.13 mmol) in toluene (1.5 mL) at −78 °C was added BBr_3 (1.0 m in hexanes; 0.15 mL, 0.15 mmol). To the resultant solution was added **6** (0.13 mmol), and the mixture was allowed to reach −20 °C. After the mixture was stirred for 19 h at −20 °C, the reaction was quenched by addition of H_2O (1 mL) and allowed to stir for 1 h at rt. The solution was made alkaline with 2 M NaOH (1.5 mL) and the resultant mixture filtered through a prepacked extraction 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** as a pale yellow oil (25 mg, 71%, ds >20:1): ^1H NMR ($CDCl_3$, 500 MHz) δ_H 7.34 (d, 2H, *J* = 7.1 Hz), 7.30 (t, 2H, *J* = 7.1 Hz), 7.22 (t, 1H, *J* = 7.1 Hz), 5.79 (ddd, 1H, *J* = 17.2, 10.3, 7.3 Hz), 5.05 (d, 1H, *J* = 17.2 Hz), 4.96 (d, 1H, *J* = 10.3 Hz), 3.85 (d, 1H, *J* = 13.4 Hz), 3.54 (d, 1H, *J* = 13.4 Hz), 3.54 (m, 1H,), 3.42 (dt, 1H, *J* = 12.0, 6.6 Hz), 3.27 (m, 1H), 3.12 (m, 1H), 3.11 (d, 1H, *J* = 7.3 Hz), 2.38 (sextet, 1H, *J* = 7.3 Hz), 2.20 (bs, 1H), 1.88−1.77 (m, 4H), 1.12 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 172.8, 140.7, 140.3, 128.22, 128.18, 126.8, 114.7, 63.1, 52.1, 46.2, 45.5, 41.4, 26.0, 24.2, 15.9; IR (neat) 3318, 2972, 2875, 1632 cm^{-1}; HRMS (CI+) calcd for $C_{17}H_{25}N_2O$ $[M + H]^+$ 273.1967, found 273.1964.

1-(2-Benzylamino-1-oxo-4-pentenyl)pyrrolidine (3a): ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.34−7.22 (m, 5H), 5.82 (ddt, 1H, *J* = 17.1, 10.1, 7.1 Hz), 5.10 (d, 1H, *J* = 17.1 Hz), 5.04 (d, 1H, *J* = 10.1 Hz), 3.83 (d, 1H, *J* = 13.1 Hz), 3.59 (d, 1H, *J* = 13.1 Hz), 3.54 (dt, 1H, *J* = 12.2, 6.7 Hz), 3.45 (dt, 1H, *J* = 12.2, 6.9 Hz), 3.36 (t, 1H, *J* = 6.8 Hz), 3.30 (dt, 1H, *J* = 9.9, 6.7 Hz), 3.21 (dt, 1H, *J* = 9.9, 6.6 Hz), 2.40−2.28 (m, 2H), 2.21 (bs, 1H), 1.92−1.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 172.7, 140.0, 134.4, 128.28, 128.26, 126.9, 117.3, 58.6, 51.8, 46.1 45.7, 37.9, 26.0, 24.1; IR (neat) 3316, 2973, 2876, 1637 cm^{-1}; HRMS (EI+) calcd for $C_{16}H_{22}N_2O$ $[M]^+$ 258.1732, found 258.1732.

(2*R,3*R**)-1-(2-Benzylamino-3-methyl-1-oxo-4-pentenyl)-pyrrolidine (*anti*-3b):** ^1H NMR ($CDCl_3$, 500 MHz) δ_H 7.31 (m, 4H), 7.22 (m, 1H), 5.89 (ddd, 1H, *J* = 17.6, 10.1, 7.2 Hz), 5.07 (d, 1H, *J* = 17.6 Hz), 5.07 (d, 1H, *J* = 10.1 Hz), 3.86 (d, 1H, *J* = 13.6 Hz), 3.57 (d, 1H, *J* = 13.6 Hz), 3.55 (m, 1H), 3.45 (m, 1H), 3.31 (m, 1H), 3.15 (d, 1H, *J* = 7.2 Hz), 3.12 (m, 1H), 2.46 (sextet, 1H, *J* = 7.2 Hz), 2.18 (bs, 1H), 1.89−1.78 (m, 4H), 1.02 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 172.6, 140.7, 140.3, 128.21, 128.17, 126.9, 114.9, 63.0, 51.9, 46.2, 45.6, 40.9, 26.1, 24.1, 16.7; IR (neat) 3327, 2971, 2875, 1632 cm^{-1}; HRMS (CI+) calcd for $C_{17}H_{25}N_2O$ $[M + H]^+$ 273.1967, found 273.1965.

(2*R,3*S**)-1-(2-Benzylamino-3-phenyl-1-oxo-4-pentenyl)-pyrrolidine (*syn*-3c):** ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.38−7.17 (m, 10H), 6.17 (ddd, 1H, *J* = 16.5, 9.7, 7.9 Hz), 5.12 (d, 1H, *J* = 16.5 Hz), 5.09 (d, 1H, *J* = 9.7 Hz), 3.81 (d, 1H, *J* = 13.4 Hz), 3.67 (t, 1H, *J* = 7.9 Hz), 3.57 (d, 1H, *J* = 13.4 Hz), 3.57 (d, 1H, *J* = 7.9 Hz), 3.49 (m, 1H), 3.38 (m, 1H), 2.90 (m, 1H), 2.63 (m, 1H), 2.04 (bs, 1H), 1.72 (m, 3H), 1.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 171.4, 141,0, 139.8, 136.9, 128.4, 128.3, 128.2, 128.2, 126.9, 126.7, 117.4, 62.2, 54.0, 51.3, 46.0, 45.5., 25.9, 24.0; IR (neat) 3325, 3060, 3028, 2974, 2951, 1633 cm^{-1}; HRMS (CI+) calcd for $C_{22}H_{27}N_2O$ $[M + H]^+$ 335.2123, found 335.2120.

(2*R,3*R**)-1-(2-Benzylamino-3-phenyl-1-oxo-4-pentenyl)-pyrrolidine (*anti*-3c):** ^1H NMR ($CDCl_3$, 500 MHz) δ_H 7.31 (m, 4H), 7.22 (m, 5H), 7.16 (m, 1H), 6.28 (ddd, 1H, *J* = 17.2, 10.3, 8.3 Hz), 5.23 (d, 1H, *J* = 17.2 Hz), 5.13 (d, 1H, *J* = 10.3 Hz), 3.90 (d, 1H, *J* = 13.6 Hz), 3.58 (d, 1H, *J* = 13.6 Hz), 3.55 (t, 1H, *J* = 8.3 Hz), 3.44 (d, 1H, *J* = 9.5 Hz), 3.33 (m, 1H), 3.09 (m, 1H), 2.78 (m, 1H), 2.42 (m, 1H), 1.58 (m, 2H), 1.43 (m, 1H), 1.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 172.0, 141.2, 140.0, 138.4, 128.4, 128.24, 128.20, 128.1, 126.9, 126.7, 117.0, 63.4, 53.2, 51.8, 45.7, 45.2, 25.7, 23.8; IR (neat) 3311, 3049, 3029, 2970, 2873, 1633 cm^{-1}; HRMS (CI+) calcd for $C_{22}H_{27}N_2O$ $[M + H]^+$ 335.2123, found 335.2120.

1-(2-Benzylamino-3,3-dimethyl-1-oxo-4-pentenyl)pyrrolidine (3e): ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.30 (m, 4H), 7.22 (m, 1H), 5.95 (dd, 1H, *J* = 17.5, 10.7 Hz), 5.01 (d, 1H, *J* = 17.5 Hz), 4.99 (d, 1H, *J* = 10.7 Hz), 3.85 (d, 1H, *J* = 13.7 Hz), 3.54 (m, 1H), 3.52 (d, 1H, *J* = 13.7 Hz), 3.40 (m, 1H), 3.25 (m, 1H), 3.01 (s, 1H), 2.99 (m, 1H), 2.09 (bs, 1H), 1.79 (m, 4H), 1.10 (s, 3H), 1.09 (s, 3H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 172.5, 145.1, 140.4, 128.16, 128.15, 126.9, 112.2, 65.2, 52.1, 46.8, 45.4, 40.5, 26.1, 24.4, 24.2, 23.1; IR (neat) 3330, 3084, 3062, 2964, 2875, 1633 cm^{-1}; HRMS (EI+) calcd for $C_{18}H_{27}N_2O$ $[M + H]^+$ 287.2123, found 287.2125.

Complex 9a: ^{1}H NMR (CD_3CN, 500 MHz) δ_H 7.55 (dd, 2H, J = 8.1, 1.7 Hz), 7.52−7.45 (m, 3H), 5.97 (ddt, 1H, J = 17.1, 10.1, 7.3 Hz), 5.63 (d, 1H, J = 17.1 Hz), 5.59 (d, 1H, J = 10.1 Hz), 4.43 (d, 1H, J = 17.3 Hz), 4.40 (d, 1H, J = 12.7 Hz), 4.25 (d, 1H, J = 12.7 Hz), 4.22 (d, 1H, J = 17.3 Hz), 3.78 (dd, 1H, J = 13.0, 7.3 Hz), 3.70 (dd, 1H, J = 13.0, 7.3 Hz), 3.50 (m, 2H), 3.40 (m, 1H), 3.29 (m, 1H), 2.00−1.79 (m, 4H); ^{11}B NMR (CD_3CN, 160 MHz) δ_B 4.9 (t, $^1J_{BF}$ = 15 Hz), −0.7 (s); ^{19}F NMR (CD_3CN, 470 MHz) δ_F −85.7 (m), −88.5 (m), −88.6 (s).

Complex 9b: ^{1}H NMR (CD_2Cl_2, 500 MHz) δ_H 7.82 (dd, 2H, J = 7.6, 1.3 Hz), 7.60−7.52 (m, 3H), 6.22 (ddt, 1H, J = 17.2, 10.0, 7.3 Hz), 5.83 (d, 1H, J = 17.2 Hz), 5.68 (d, 1H, J = 10.0 Hz), 5.10 (d, 1H, J = 13.0 Hz), 4.85 (d, 1H, J = 16.7 Hz), 4.68 (d, 1H, J = 13.0 Hz), 4.66 (d, 1H, J = 16.7 Hz), 4.34 (m, 1H), 4.20 (m, 1H), 3.89 (m, 1H), 3.72 (m, 2H), 3.50 (m, 1H), 2.20−1.94 (m, 4H); ^{11}B NMR (CD_2Cl_2, 160 MHz) δ_B 5.7 (s).

Pyrrolidine 10a. To a stirred solution of *syn*-**3b** (9 mg, 0.033 mmol) in THF (0.5 mL) was added $Hg(CF_3CO_2)_2$ (25 mg, 0.058 mmol) in THF (1 mL) and the resultant solution heated at reflux for 1.5 h. The reaction mixture was cooled to 0 °C, 0.5 M $NaBH_4$/2 M NaOH (1.5 mL) was added, and the mixture was stirred at rt for 2.5 h. The mixture was diluted with Et_2O and centrifuged. The dried (K_2CO_3) organic phase was concentrated and chromatographed (pentane/EtOH 18:1 → 9:1 + 1% NH_3) to provide **10a** (5.4 mg, 60%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.32−7.20 (m, 5H), 3.89 (d, 1H, J = 12.9), 3.66 (d, 1H, J = 12.9), 3.47 (m, 2H), 3.38 (d, 1H, J = 8.5), 3.17 (m, 2H), 2.88 (m, 1H), 2.67 (dt, 1H, J = 8.5, 7.3), 2.45 (m, 1H), 1.98 (m, 1H), 1.77 (m, 5H), 0.93 (d, 3H, J = 7.3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 170.4, 138.7, 129.3, 128.0, 126.9, 66.5, 57.5, 52.8, 46.1, 45.4, 35.3, 32.3, 26.3, 24.0, 16.3; IR (neat) 3025, 2965, 1623 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{25}N_2O$ [M + H]$^+$ 273.1967, found 273.1971.

Pyrrolidine 10b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.31−7.20 (m, 5H), 3.83 (d, 1H, J = 12.9 Hz), 3.59 (d, 1H, J = 12.9 Hz), 3.54 (m, 1H), 3.40 (m, 2H), 3.14 (m, 2H), 3.00 (d, 1H, J = 6.7 Hz), 2.55 (m, 1H), 2.41 (m, 1H), 2.15 (m, 1H), 1.76 (m, 4H), 1.42 (m, 1H), 1.10 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 171.8, 138.9, 129.0, 128.0, 126.9, 73.3, 58.3, 52.9, 46.2, 46.1, 37.9, 32.2, 26.3, 23.8, 20.1; IR (neat) 3052, 2959, 1631 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{25}N_2O$ [M + H]$^+$ 273.1967, found 273.1968.

Pyrrolidine 11: ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.35−7.19 (m, 10H), 5.01 (m, 1H), 3.94 (d, 1H, J = 12.7 Hz), 3.88 (d, 1H, J = 8.2 Hz), 3.75 (d, 1H, J = 12.7 Hz), 3.74 (m, 1H), 3.50 (t, 1H, J = 8.2 Hz), 3.27 (m, 1H), 3.00 (m, 1H), 2.97 (dd, 1H, J = 9.2, 4.9 Hz), 2.50 (m, 1H), 2.32 (m, 1H), 1.74 (d, 1H, J = 5.0 Hz), 1.49 (m, 2H), 1.32 (m, 1H), 1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 169.4, 137.3(×2), 129.2, 128.8, 128.2, 128.1, 127.3, 127.0, 76.2, 67.3, 60.2, 56.9, 56.2, 45.5, 45.1, 25.7, 23.7; IR (neat) 3381, 2950, 1631, 1451, 1081 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{27}N_2O_2$ [M + H]$^+$ 351.2073, found 351.2078.

Acknowledgment. This work was supported financially by the Swedish Research Council. We also gratefully acknowledge Dr. Colin Ray from AstraZeneca, Södertälje, for his careful proof reading of the manuscript.

Supporting Information Available: Synthesis and characterization of **2**. ^{1}H and ^{13}C NMR spectra for **2**, **3**, **7**, **8**, **10a**,**b**, **11**, **12**, **14b**−**e**, **15b**−**e**, and **16b**−**e**; ^{1}H, ^{11}B, and ^{19}F NMR spectra for **9a**; ^{1}H and ^{11}B NMR spectra for **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035618G