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NMR Investigations on Boron Complexes in the Conjugate Addition on α,*β*-Unsaturated Imides

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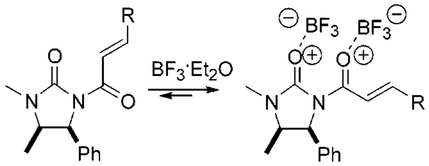
ABSTRACT



The 1,4-addition of *O*-benzylhydroxylamine to α,*β*-unsaturated imide 1 in the presence of $BF_3{\cdot}Et_2O$ proceeds with the preferential attack of the nucleophile on the C*β*-re face. To explain this unexpected reactivity ^1H, ^{13}C, and ^{11}B NMR investigations have been carried out on the boron–imide complex, which show the presence of an *S*-*cis* imide chain conformation.

Numerous recent studies make use of Lewis acids to catalyze organic reactions.[1] The 1,4-addition of nucleophiles to α,*β*-unsaturated carboxylic acid derivatives has proven to be a useful method for the asymmetric induction at the *β*-carbon with carbon−carbon or carbon−heteroatom bond formation.[2] In this context, the conjugate addition of amines to α,*β*-unsaturated carbonyl compounds is one of the most popular and useful procedures for the synthesis of optically active *β*-amino acids.[3] When we began this study with the aim of preparing chiral *β*-amino acids, we obtained a good degree of asymmetric induction in the addition of *O*-benzylhydroxylamine to chiral imides in the presence of Lewis acid by using 1,5-dimethyl-4-phenylimidazolidin-2-one as chiral auxiliary.[4] Lewis acids greatly enhance the electrophilicity of the *β*-carbon, lowering the molecular orbitals of α,*β*-unsaturated compounds, and ensure a good diastereofacial control by blocking the substrate in a dominant reactive conformer.[5]

The ^1H NMR spectra of α,*β*-unsaturated derivatives and Lewis acids give useful information on the complex, based on the chemical shift changes.[6] Accordingly, NMR experiments on Et_2AlCl−imide complexes carried out contemporaneously by Castellino[6b] and us[4] show chemical shift changes between the ground state of the substrate and the aluminum−substrate complex, in agreement with a chelated structure as reported in Figure 1.

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[1] For a review on Lewis acid promoted addition to carbonyl compounds, see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. (b) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989−990.

[2] For a review on conjugate additions, see: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem*. **1991**, *20*, 87−170. (b) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, pp 1−236. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (d) Perlmutter, P. In *Advances in Asymmetric Synthesis;* Stephenson, G. R., Ed.; Chapman & Hall: London, 1996; pp 222−230. (e) Leonard, J.;Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051−2061. (f) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.

[3] (a) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274−6282. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (c) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3−11. (d) Cardillo, G., Tomasini, C. *Chem. Soc. Rev.* **1996**, 117−128. (e) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616.

[4] Amoroso, R., Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615−5619.

[5] (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

[6] (a) Laszlo, P.; Teston, M. *J. Am. Chem. Soc*. **1990**, *112*, 8750−8754. (b) Castellino, S., Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987. (c) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem* **1982**, *60*, 801−808.

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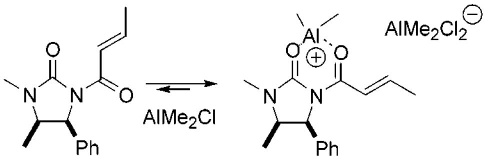
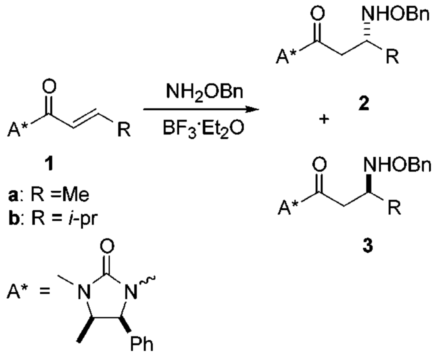


Figure 1. Aluminum−α,*β*-unsaturated imide complex.

On pursuing our studies on the 1,4-addition of *O*-benzylhydroxylamine to unsaturated imides (Scheme 1), we performed the reaction in the presence of $BF_3 \cdot Et_2O$. Some results are reported in Table 1.

Scheme 1. 1,4-Addition of *O*-Benzylhydroxylamine to Imide **1**



These results are a real surprise since $BF_3 \cdot Et_2O$ has only one coordination site and should thus be incapable of chelation. On the other hand, the chelation-controlled product **2** was obtained as the major isomer in the reaction with $BF_3 \cdot Et_2O$. The same compound was obtained when $AlMe_2Cl$ or $MgBr_2$ was utilized in this kind of reaction. Since boron has long been regarded as a non-chelating Lewis acid, in an effort to rationalize the course of the reaction and, in particular, to explain the analogous reactivity between $AlMe_2Cl$ and $BF_3 \cdot Et_2O$, we carried out the following model. First of all we examined the ^{1}H NMR[7] behavior of imides **1a** and **1b** after adding 1 equiv of $BF_3 \cdot Et_2O$ in CD_2Cl_2. These experiments show the presence of two species that evolve toward a sole complex after adding another equivalent of $BF_3 \cdot Et_2O$. This last complex, which is present in both **1a**−$BF_3 \cdot Et_2O$ (1 equiv) and in **1a**−$BF_3 \cdot Et_2O$ (2 equiv), is in our opinion the reactive one and it is responsible for the diastereomeric ratio. The ^{1}H NMR spectra of **1a**, **1a**−$BF_3 \cdot Et_2O$ (1 equiv), and **1a**−$BF_3 \cdot Et_2O$ (2 equiv) are reported in Figure 2.

Table 1. 1,4-Addition of *O*-Benzylhydroxylamine to Unsaturated Imides

entry	imide	$BF_3 \cdot Et_2O$ (equiv)	*t* (h)	yield[a] (%)	dr[a] **2/3**
1	**1a**	1	70	80	90:10
2	**1a**	2	70	>95	90:10
3	**1b**	1	72	40[b]	90:10
4	**1b**	2	72	60[b]	90:10

[a] Calculated by ^{1}H NMR. All the reactions were carried out in CH_2Cl_2 from −40 °C to rt. [b] The unreacted starting material was recovered from the reaction.

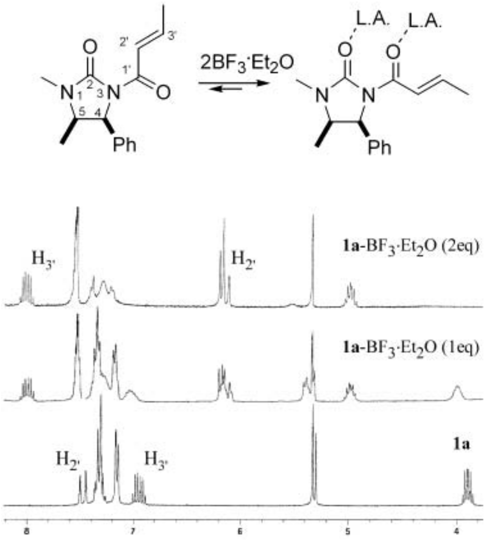


Figure 2. ^{1}H NMR of **1a**− and **1a**−$BF_3 \cdot Et_2O$ complex.

The ^{1}H NMR spectra suggest the coordination of both carbonyl groups C2 and C1′ since $H_{2'}$ and $H_{3'}$ are respectively shielded and deshielded, in agreement with a preferential *S-cis* conformation of the unsaturated imide chain.[4] This situation favors a preferential attack from the C*β*-re face, as confirmed by the results reported in Table 1. The ^{1}H NMR data related to imidates **1a** and **1b** are reported in Table 2.

Table 2. ^{1}H NMR Data for α,*β*-Unsaturated Imide Complexes with $BF_3 \cdot Et_2O$ (2 equiv)

imide	$H_{2'}$	$H_{3'}$	$H_{4'}$	H_4	H_5
1a	7.47	6.95	1.90	5.30	3.89
1a−$BF_3 \cdot Et_2O$	6.13	7.98	2.08	6.18	4.97
1b	7.42	6.90	2.50	5.32	3.90
1b−$BF_3 \cdot Et_2O$	5.97	7.90	2.57	6.21	4.97
A*				4.77	3.89
A*−$BF_3 \cdot Et_2O$				5.13	4.19

On the basis of this observation, we tried to examine the real coordination between $BF_3 \cdot Et_2O$ and the substrates, taking into account three possible situations: (a) the chelation of

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[7] NMR spectra were recorded with a Gemini Varian 300 MHz spectrometer. Chemical shifts were reported as δ values relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ ppm (^{1}H NMR) or $\delta = 77.0$ ppm (^{13}C NMR). For ^{11}B spectra, $BF_3 \cdot Et_2O$ was taken as external reference at $\delta = 0$ ppm.

both carbonyls with a BF_3 molecule, with formation of a pentacoordinate boron complex; (b) the chelation of both carbonyls with a BF_3 molecule, with displacement of a fluorine and formation of a BF_4^- molecule; (c) the coordination of each carbonyl with one molecule of BF_3 with formation of a “U-shaped” complex where electrostatic attraction simulate chelation.

Recently Maruoka and co-workers[8] reported that boron and aluminum are capable of forming pentacoordinate chelate-type complexes in certain reaction systems. To prove the hypothetical existence of pentacoordinate boron fluoride complexes, we carried out further investigations. The ^{13}C NMR studies performed on **1a**− and **1b**−$BF_3 \cdot Et_2O$ (2 equiv), recorded at 20 °C, confirm that the carbonyl C1′ is significantly deshielded by the boron coordination, while the carbonyl 2 shows only a slight chemical shift change (Table 3). To verify why this carbonyl group is quite unchanged by the presence of boron trifluoride, the ^1H and ^{13}C NMR spectra of the 1,5-dimethyl-4-phenylimidazolidin-2-one alone and with 1 equiv of $BF_3 \cdot Et_2O$ were recorded in CD_2Cl_2. The comparison of ^1H chemical shifts of the ground state and the complex showed a deshielding of H_4 and H_5 of 0.3 ppm (Table 2), while only small changes were observed in ^{13}C NMR chemical shifts. Indeed, only a shift of 1 ppm was observed for the signal relative to carbonyl C2, confirming a slight effect of the boron coordination on this position (Table 3). On the basis of ^{13}C results, the pentacoordination of boron may not be ruled out and further investigations have been made through ^{11}B NMR.[9] The spectra were recorded at rt, at − 40 °C, and at −60 °C, taking $BF_3 \cdot Et_2O$ (0 ppm) as external reference. The spectrum of **1**−$BF_3 \cdot Et_2O$ (2 equiv) showed a unique signal at −0.9 ppm at room temperature, while a second signal at 0 ppm was observed when an excess of $BF_3 \cdot Et_2O$ was added in the same sample. On the other hand, the signal at 0 ppm was already present when the spectra were recorded at − 40 and −60 °C; this signal increased when $BF_3 \cdot Et_2O$ was added in excess.

Table 3. ^{13}C NMR Data for α,*β*-Unsaturated Imide Complexes with $BF_3 \cdot Et_2O$ (2 equiv)

imide	$C_{4'}$	$C_{2'}$	$C_{3'}$	C_2	$C_{1'}$
1a	18.5	123.6	144.1	156.0	164.7
1a−$BF_3 \cdot Et_2O$	21.1	116.4	167.9	155.3	170.1
1b	31.6	119.6	155.1	156.1	165.1
1b−$BF_3 \cdot Et_2O$	33.9	112.9	176.6	155.2	170.6
A*				162.3	
A*−$BF_3 \cdot Et_2O$				161.0	

On the basis of these results, the preferential hypothesis of a boron tetracoordination instead of a boron pentacoordination is advanced.[10] Furthermore, the presence of a unique boron signal disfavors the possibility of formation of BF_4^-, obtained from the displacement of fluorine.[11]

Therefore, in conclusion, we propose the coordination of each carbonyl group with a BF_3 molecule that allows the *syn* conformation of the substrate imide, in which electrostatic attractions between BF_3 at C1′ and the partially positive carbonyl moiety could simulate chelation (Figure 3).

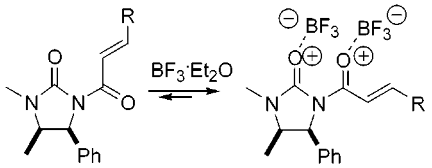

Figure 3. α,*β*-Unsaturated imide complex with $BF_3 \cdot Et_2O$ (2 equiv).

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Supporting Information Available: The ^1H, ^{13}C, and ^{11}B spectra of compounds **1a** and **1b** and of the boron complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] (a) Maruoka, K.; Ooi, T. *Chem. Eur. J.* **1999**, *3*, 829−833. (b) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1998**, *120*, 5327−5328.

[9] Parks, D. J.; Piers, W. E.; Parvez, M.; Atencio, R.; Zaworotko, M. J. *Organometallics* **1998**, *17*, 1369−1377 and references therein.

[10] Lee, D. Y.; Martin, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 5745−5746.

[11] Mann, B. E. In *NMR and the Periodic Table*; Harris, R. K., Mann, B. E., Eds.; Academic Press: London, 1978; pp 91−93.