# Chiral Lewis Acid Catalysis in Conjugate Additions of *O*-Benzylhydroxylamine to Unsaturated Amides. Enantioselective Synthesis of β-Amino Acid Precursors

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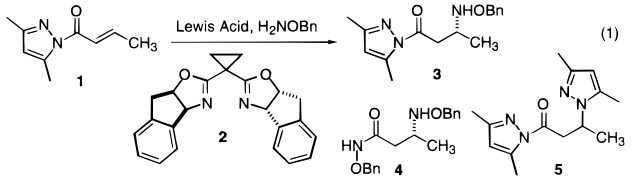
There has been an increasing interest in simple and functionalized β-amino acids and their derivatives.[1,2] A potentially straightforward methodology for their synthesis is the conjugate addition of nitrogen nucleophiles to α,β-unsaturated derivatives. Diastereoselective additions in which the nitrogen nucleophile or the α,β-unsaturated substrate is chiral have been reported in the literature.[3] However, only one report[4] of chiral Lewis acid-catalyzed additions of amines has appeared (maximum ee of 42%).[5] We disclose here high levels of enantioselectivity in the conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated pyrazole amides using catalytic amounts of a chiral Lewis acid prepared from $MgBr_2 \cdot OEt_2$ and a bisoxazoline. We also show that the opposite enantiomer of the product can be selected by a simple change of the Lewis acid. Furthermore, in at least one example the kinetic enantioselectivity can be enhanced by preferential destruction of the minor enantiomer.

We have recently described enantioselective free radical-mediated conjugate additions to α,β-unsaturated derivatives with chiral Lewis acids.[6] We were intrigued by the potential of these chiral Lewis acid/unsaturated amide combinations toward the addition of amines. Our experiments began with the addition of *O*-benzylhydroxylamine (1.1 equiv) to the pyrazole-derived crotonamide **1** in the presence of stoichiometric amounts of the chiral Lewis acid prepared from $MgBr_2 \cdot OEt_2$ and bisoxazoline **2** (eq 1 and Table 1).[7] The conjugate addition was relatively slow




at low temperatures (entry 1, Table 1)[8] as evidenced by low conversions after a short time. The enantioselectivity of the addition product (**3**) was good (79%). Increasing the reaction time improved the chemical yield whereas the ee of **3** remained the same (entry 2). Continuation of the reaction for another 24 h led to a small increase in yield but with a steep rise of ee (entry 3).[9] The highest ee (97%) was obtained after 72 h. Next the effect of temperature and the stoichiometry of the chiral Lewis acid on the reaction were investigated. Increasing the reaction temperature to −60 °C led to faster reaction times with similar chemical yields and ee's (compare entry 5 with 4). Further warming to 0 °C led to enhancement of reaction rate with concomitant lowering of the yield of **3** and its ee (entry 6). The conjugate addition was equally effective with catalytic amounts of the Lewis acid (entries 7 and 8). *These constitute the first examples of highly enantioselective conjugate amine additions using catalytic amounts of chiral Lewis acids*.

**Table 1.** Conjugate Addition of *O*-Benzylhydroxylamine to Crotonamide **1**[a]

| entry | Lewis acid (eqs) | Eqs. LA | temp, °C | time, h | yield, %[b] | ee, %[c] (config) |
|---|---|---|---|---|---|---|
| 1 | $MgBr_2$ | 1.0 | −80 | 1.5 | 39 | 79 (*R*) |
| 2 | $MgBr_2$ | 1.0 | −80 | 17 | 53 | 80 (*R*) |
| 3 | $MgBr_2$ | 1.0 | −80 | 48 | 57 | 91 (*R*) |
| 4 | $MgBr_2$ | 1.0 | −80 | 72 | 60 | 97 (*R*) |
| 5 | $MgBr_2$ | 1.0 | −60 | 21 | 62 | 96 (*R*) |
| 6 | $MgBr_2$ | 1.0 | 0 | 2 | 59 | 61 (*R*) |
| 7 | $MgBr_2$ | 0.3 | −60 | 22 | 80 | 92 (*R*) |
| 8 | $MgBr_2$ | 0.1 | −60 | 22 | 87 | 88 (*R*) |
| 9 | $Y(OTf)_3$ | 1.0 | −60 | 22 | 67 | 59 (*S*) |
| 10 | $Yb(OTf)_3$ | 1.0 | −60 | 22 | 78 | 41 (*S*) |

[a] For reaction conditions see Supporting Information. [b] Isolated yields after chromatography. [c] ee's were determined by chiral HPLC analysis. The configuration of **3** was established by converting it to known 3-*N*-benzoylamino methyl butyrate.

We have examined a few other Lewis acids in the conjugate addition.[10] Of these, the lanthanide triflates provide good chemical yields and moderate enantioselectivity (entries 9 and 10). The most significant outcome of the lanthanide triflate experiments are that they provide the addition product with opposite configuration to the one obtained by the use of $MgBr_2$ as the Lewis acid (compare entries 9 and 10 with 5). *Thus we can obtain either of the two enantiomers by a simple change of the Lewis acid.*

The experiments in entries 1−4 in Table 1 indicate that increases in ee correlate with decreases in yields. A careful product analysis showed that besides **3**, a product (**4**) from the amidolysis of **3** and a product (**5**) arising from conjugate addition of 3,5-dimethylpyrazole to **1** were also formed in varying amounts {for entry 5, **3** (62%, 96% ee); **4** (22%, 60% ee), and **5** (3−5%)}.[11]

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(1) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1836 and references therein. Also see: *Chem. Eng. News* **1997**, June 16.

(2) For a discussion of the synthesis and biology of β-amino acids see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. For comprehensive reviews see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. Guenard, D.; Gueritte-Voegelein, R.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160. Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630. Miura, K.; Sawa, T.; Takeuchi, T.; Umezawa, H. *J. Antibiotics* **1986**, *39*, 734. Blomgren, H.; Wasserman, J. *J. Can. Lett.* **1981**, *11*, 303. Iizuka, K.; Kamijo, T.; Kubota, T.; Akahane, K.; Umeyama, H.; Kiso, Y. *J. Med. Chem.* **1988**, *31*, 701.

(3) For general information see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. For selected examples see: (a) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455. (b) Davies, S. G.; Fenwick, D. T. *J. Chem. Soc., Chem. Commun.* **1995**, 1109. (c) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615. (d) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293.

(4) (a) Falborg, L.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823. (b) For an achiral Lewis acid-catalyzed conjugate addition see: Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827. (c) For chiral Lewis acid-catalyzed conjugate addition of thiols see: Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

(5) For the synthesis of β-amino acids (esters) or β-lactams using chiral Lewis acid but not involving conjugate amine addition see: Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

(6) (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (b) Sibi, M. P.; Ji, J.; Wu, J.; Gurtler, S.; Porter, N. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (c) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955.

(7) The ligand **2** is readily prepared from amino indanol. See Supporting Information. We have only examined a few bisoxazoline ligands in the conjugate addition. For seminal contributions of bisoxazoline ligands see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. For a recent review see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymm.* **1998**, *9*, 1.

(8) Non-Lewis acid-mediated background additions are <5% at these temperatures.

(9) Several control and crossover experiments indicate that the conjugate additions are irreversible. See Supporting Information.

(10) $MgI_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $ZnBr_2$, and $Sn(OTf)_2$ gave lower yields and/or lower selectivity.

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**Table 2.** Enantioselective Amidolysis of Racemic **3**[a]

$$\text{racemic } \mathbf{3} \xrightarrow[CH_2Cl_2,\ \text{ligand } \mathbf{2}]{MgBr_2,\ H_2NOBn} (R)\text{-}\mathbf{3} + (S)\text{-}\mathbf{4} \qquad (2)$$

| entry | chiral LA, Eqs | amine Eqs | time, h | **3**, % yield (ee)[b,c] | **4**, % yield (ee)[b,c] |
|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | 3 | 36 (52) (*R*) | 46 (30) (*S*) |
| 2 | 1.0 | 0.5 | 3 | 47 (47) (*R*) | 34 (60) (*S*) |
| 3 | 0.3 | 0.5 | 24 | 71 (6) (*R*) | 24 (36) (*S*) |

[a] For reaction conditions see Supporting Information. [b] Isolated yields after chromatography. [c] ee's were determined by chiral HPLC analysis.

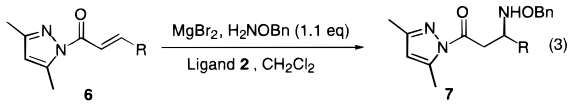
While the major enantiomer of **4** was also *R* as was **3**, the enantiomeric ratio was much lower, indicating a kinetic resolution. *Apparently the minor enantiomer undergoes faster amidolysis leading to enhanced enantioselectivity of the surviving* ***3*** *and also accounting for its reduced chemical yield.*[12]

To substantiate this explanation, the amidolysis of racemic **3** with chiral Lewis acid was investigated (Table 2, eq 2). Treatment of racemic **3** with stoichiometric amounts of the chiral Lewis acid and the amine for 3 h indeed gave the expected (*R*)-enriched **3** and the (*S*)-enriched product **4** (entry 1).[13] Reducing the amount of the amine to half an equivalent led to an increase in the ee of the product (entry 2). Use of a substoichiometric amount of the Lewis acid led to lower conversion (entry 3).

A variety of substrates were found to undergo chiral Lewis acid-mediated *O*-benzylhydroxylamine addition. The reactions proceeded with high yields and enantioselectivity with a stoichiometric amount of the Lewis acid (Table 3, entries 1−5; eq 3).[14] The use of 30 mol % catalyst was found to be optimal for obtaining high chemical yields as well as selectivity. At this loading, the chemical yields were higher because product destruction by amidolysis was minimal. At lower catalytic loading (10 mol %) unhindered substrates (entries 1, 2, and 4) gave similar results as those with 30 mol % catalyst. Substrates with increased steric size at the $\beta$-carbon required higher temperatures for efficient conversions at 10 mol % loading leading to slightly lower chemical yields and selectivity (entries 3 and 5). The cinnamide **6e** gave low chemical yields but good enantioselectivity with 100 and 30 mol % catalyst but was unreactive using 10 mol % catalyst.

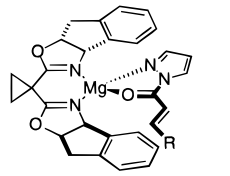
A working hypothesis for the selectivity observed with $MgBr_2$ is presented. A *re* face amine addition to an *s-cis*-substrate/Lewis acid/ligand complex with a tetrahedral or a cis octahedral arrangement accounts for the observed product configuration (Figure 1). In general, this addition proceeds with an approximate 15:1 enantioselectivity as shown by experiments in which amidolysis is minimal (entries 1−5, Table 3, 30 mol % catalyst).

**Table 3.** Conjugate Addition of *O*-Benzylhydroxylamine to Amides[a]




| | | chiral Lewis acid, % yield (ee)[a] | | |
|---|---|---|---|---|
| entry | R | 100 mol %[b] | 30 mol %[b] | 10 mol % |
| 1 | Me (**3**) | 62 (96) | 80 (92) | 87 (88)[d] |
| 2 | Et (**7a**) | 56 (92) | 74 (92) | 84 (88)[d] |
| 3 | $CH_2C_6H_{11}$ (**7b**) | 39 (90) | 53 (90) | 57 (70)[e] |
| 4 | $CH_2Ph$ (**7c**) | 62 (96) | 80 (95) | 85 (90)[d] |
| 5 | i-Pr (**7d**) | 41 (83) | 76 (87) | 56 (67)[e] |
| 6 | Ph (**7e**) | 21 (78)[c] | 24 (83) | <3%[d] |

[a] For reaction conditions see Supporting Information. Yields are for isolated and column purified material. The amounts of amidolysis and/or pyrazole addition products have not been determined. ee's were determined by chiral HPLC analysis. [b] Reactions were carried out at −60 °C for 20−22 h for entries 1−5 and 72 h for entry 6. [c] 60% of the starting material was recovered. [d] Reactions were carried out at −25 °C for 16−17 h for entries 1, 2, and 4 and 72 h for entry 6. [e] Reactions were carried out at ambient temperatures for 6 h.




The 3,5-dimethyl groups and the Mg counterions are not shown

**Figure 1.**

The catalytic nature of the reaction shows that the substrate competes favorably with the product as a Lewis base enabling turnover. Under stoichiometric conditions, both substrate and the product are bound to the Lewis acid and some amidolysis occurs resulting in reduced chemical yield. Under catalytic conditions, product is not activated by Lewis acid until the substrate is almost exhausted such that amidolysis is minimal until addition is nearly complete. The origin of the reversed sense of stereoinduction with lanthanide Lewis acids remains unclear. Experiments are underway with other amine nucleophiles[15] and achiral templates.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **1**−**7** (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) The stereochemistry of **5** was not determined.

(12) Acylpyrazoles undergo esterification readily in the presence of Lewis acids, see: Kashima, C.; Harada, H.; Kita, I.; Fukuchi, I.; Hosomi, A. *Synthesis* **1994**, 61. The configuration of **3** was established by converting it to known 3-*N*-benzoylamino methyl butyrate. For a procedure see ref 4a.

(13) Results suggest an ~5:1 rate preference for the *S* enantiomer.

(14) The required starting materials were prepared by standard procedures. See Supporting Information for details.

(15) Preliminary results show that aminodiphenylmethane adds to **1** in 30% chemical yield and 75% ee.