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N-Benzylhydroxylamine Addition to β-Aryl Enoates. Enantioselective Synthesis of β-Aryl-β-amino Acid Precursors

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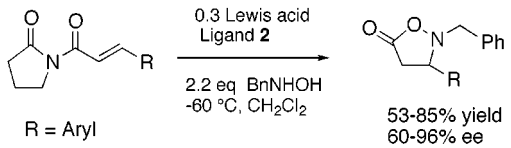
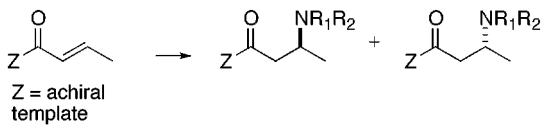
ABSTRACT



Chiral Lewis acid catalyzed *N*-benzylhydroxylamine addition to pyrrolidinone-derived enoates afforded β-aryl-β-amino acid derivatives in high enantiomeric purity with moderate to very good chemical efficiency.

β-Amino acids are important segments of a variety of bioactive natural products.[1] They also serve as precursors for the synthesis of β-lactams.[2] Given their significance, the development of efficient methods for their synthesis is important. A common approach for the synthesis of β-amino acids is the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carboxylic acid derivatives (Scheme 1).

Scheme 1



Stereoselective additions utilizing either chiral nucleophiles or chiral enoates have been reported in the literature, most notably from the groups of Davies, d'Angelo, Enders, Cardillo, and others.[3] However, only few examples of chiral Lewis acid catalyzed amine additions have been reported. We have recently developed a novel catalytic method for enantioselective synthesis of β-amino acid using *O*-benzylhydroxylamine as the nucleophile. Good isolated yields and excellent levels of enantioselectivity were obtained.[4] Chiral (salen)Al(III) complex catalyzed conjugate addition of hydrazoic acid (HN_3) to α,β-unsaturated imines was recently described by Jacobson et al.[5]

β-Aryl-substituted β-amino acids have also received extensive scrutiny.[6] The chiral Lewis acid methodologies described above are applicable to a variety of alkyl substit-

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uents at the β-carbon. However, β-aryl groups fail to provide adequate results.[7] They are considerably less reactive than the corresponding β-alkyl substrates. This lack of reactivity intrigued us and alternate pathways were considered; the successful results from these endeavors are presented here.

N-Substituted hydroxylamines are excellent nucleophiles in conjugate addition to α,β-unsaturated enoates.[8] Isoxazolidinones are formed directly in these reactions.[9] Zhao et al. have studied the conjugate addition of *N*-alkylhydroxylamine to enoates in some detail and have proposed a concerted mechanism for the reaction.[10]

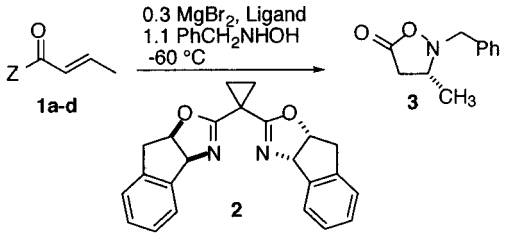
In an effort to improve the reactivity of β-aryl derivatives in conjugate addition reactions, we hypothesized that the use of a more reactive achiral template and/or a more reactive amine nucleophile was necessary. Additionally, the formation of the same isoxazolidinone irrespective of the starting achiral template would simplify product analysis. Our experiment began with the conjugate addition of *N*-benzylhydroxylamine to a series of crotonamides **1**. Magnesium-based Lewis acids and a bisoxazoline derived from aminoindanol, a combination which has been successful in our previous work, were employed as the catalyst. In contrast to the high selectivity (96%ee) observed with *O*-benzylhydroxylamine addition to 3,5-dimethylpyrazole crotonate,[4] reactions with *N*-benzylhydroxylamine (entry 1, Table 1) proceeded only with moderate selectivity.

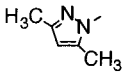
We were also interested in exploring other achiral templates. Oxazolidinone and pyrrolidinone have proven to be outstanding achiral templates in a variety of enantioselective transformations.[11] Higher levels of selectivity were obtained for the conjugate addition to pyrrolidinone- and oxazolidinone-derived crotonamides **1b**−**d** (entries 2−4, Table 1). Several other trends are also noteworthy. Pyrrolidinone substrates **1c** and **1d** (entries 3 and 4) are more reactive than the pyrazole substrate **1a**. Under the same reaction conditions, reactions with *N*-benzylhydroxylamine are much faster (entry 1) as compared to addition of *O*-benzylhydroxylamine.[12]

Two additional *N*-substituted hydroxylamines, *N*-benzhydryl- and *p*-methoxybenzylhydroxylamine, were evaluated. Pyrrolidinone crotonate (**1c**) was chosen as the achiral substrate in this study. The results are tabulated in Table 2.

We were hoping that the bulkier *N*-benzhydrylhydroxylamine would be more sensitive to steric interactions and thus provide higher levels of selectivity. Additionally, the *N*-substituents (benzhydryl and *p*-methoxybenzyl) would pro-

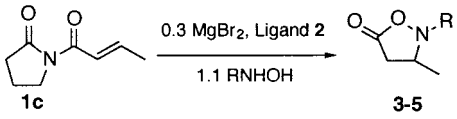
Table 1. *N*-Benzylhydroxylamime Conjugate Addition. Effect of Achiral Templates



entry	template (Z)	time (h)	yield[a] (%)	ee[b,c] (%)
1a		12	74	73 (*R*)
1b		11	74	92 (*R*)
1c		8	83	85 (*R*)
1d		6	55	89 (*R*)

[a] Isolated yields after chromatography. [b] ee's were determined by chiral HPLC analysis. [c] The configuration of **3** was established by converting it to known 3-aminobutyric acid by comparing the sign of rotation of the product acid with that reported in the literature.[3d]

Table 2. Conjugate Addition to Pyrrolidinone Crotonate. Effect of Amine Nucleophiles



R	prod.	time (h)	yield (%)[a]	ee (%)[b]
$PhCH_2$	**3**	8	80	86
$(Ph)_2CH$	**4**	21	90	85
$4\text{-}MeOC_6H_4CH_2$	**5**	24	78	86

[a] Isolated yields after chromatography. [b] ee's were determined by chiral HPLC analysis.

(6) Isolation of β-DOPA: von Nussbaum, F.; Spiteller, P.; Rüth, M.; Steglich, W.; Wanner, G.; Gamblin, B.; Stievano, L.; Wagner, F. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3292. (b) Coleman, P. J.; Hutchinson, J. H.; Hunt, C. A.; Lu, P.; Delaporte, E.; Rushmore, T. *Tetrahedron Lett.* **2000**, *41*, 5803. (c) For the use of β-aryl amino acids in Fibrinogen receptor antagonists, see: Stilz, H. U.; Jablonka, B.; Just, M.; Knolle, J.; Paulus, E. F.; Zoller, G. *J. Med. Chem.* **1996**, *39*, 2118.

(7) For an example of enantioselective catalytic hydrogenation leading to β-aryl-β-amino acids, see: Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.

(8) (a) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179. (b) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291. (c) Ishikawa, T.; Nagai, K.; Senzaki, M.; Tatsukawa, A.; Saito, S. *Tetrahedron* **1998**, *54*, 2433. (d) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363. (e) Stamm, H.; Steudle, H. *Tetrahedron Lett.* **1976**, 3607. (f) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3945. (g) Keen, S. P.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 4307. (h) Jurczak, M.; Socha, D.; Chmielewski, M. *Tetrahedron* **1996**, *52*, 1411. (i) Socha, D.; Jurczak, M.; Chmielewski, M. *Tetrahedron* **1997**, *53*, 739.

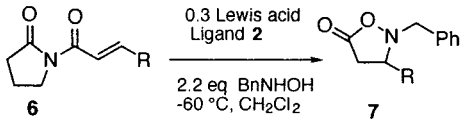
(9) For the conversion of isoxazolidinones to β-amino acids, see: Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041.

(10) (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. (b) Xiang, Y.; Gi, H.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 7430. (c) Pan, S.; Wang, J.; Zhao, K. *J. Org. Chem.* **1999**, *64*, 4.

(11) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, 1996.

(12) Typical reaction time for *O*-benzylhydroxylamine additions was 21−22 h at −60 °C (see ref 4 for details).

Table 3. Conjugate Addition with *N*-Benzylhydroxylamine as a Nucleophile. Effect of β-Aryl Substituent

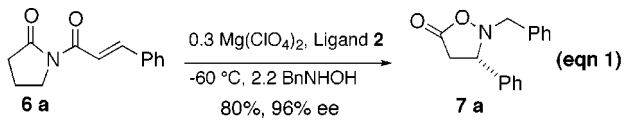


entry	R	Lewis acid	time (h)	yield (%)[a]	ee (%)[b,c]
6a	Ph-	MgI_2	48	80	85
		$Mg(ClO_4)_2$	48	80	96
6b	4-$MeOC_6H_4$-	MgI_2	67	66	90
		$Mg(ClO_4)_2$	87	65	80
6c	4-$NO_2C_6H_4$-	MgI_2	42	60	88
		$Mg(ClO_4)_2$	42	60	91
6d	4-ClC_6H_4-	MgI_2	38	85	91
		$Mg(ClO_4)_2$	34	87	96
6e		MgI_2	93	53	81
		$Mg(ClO_4)_2$	72[d]	72	60
6f		MgI_2	60	80	91
		$Mg(ClO_4)_2$	60	70	90
6g		MgI_2	55	58	93
		$Mg(ClO_4)_2$	50	62	95

[a] Isolated yields after chromatography. [b] ee's were determined by chiral HPLC analysis. [c] The configuration of **7a** was established by converting it to a known compound (see Supporting Information). [d] Reaction was carried out at −45 °C.

vide alternate pathways for deprotection. Similar selectivity was obtained for all the three *N*-substituted hydroxylamines. *N*-Benzhydrylhydroxylamine was less reactive than *N*-benzylhydroxylamine (compare entries 1 and 2, Table 2), and this was probably due to its bulkiness. Among the three hydroxylamines examined, *N*-benzylhydroxylamine showed the highest reactivity in the conjugate addition reactions.

Taking advantage of the high reactivity of *N*-benzylhydroxylamine, we then carried out conjugate addition reactions on cinnamates. A survey of the achiral templates at 0 °C revealed that pyrrolidinone cinnamate gave the highest reactivity.[13] However, at −60 °C, conjugate addition of *N*-benzylhydroxylamine to all three cinnamate substrates using $MgBr_2 \cdot Et_2O$ as the Lewis acid were slow; reactions were incomplete after 48 h. We have also examined several other Lewis acids: MgI_2 and $Mg(ClO_4)_2$. At 0 °C, all three magnesium Lewis acids showed similar reactivity,[14] and ee's ranging from 66% to 76% were obtained. However, at −60 °C, reactions using MgI_2 and $Mg(ClO_4)_2$ as the Lewis acid proceeded much faster than reactions catalyzed by $MgBr_2 \cdot Et_2O$. The best result was obtained for the conjugate addition of *N*-benzylhydroxylamine to pyrrolidinone cinnamate (**6a**) catalyzed by $Mg(ClO_4)_2$ and bisoxazoline ligand **2** (eq 1). The absolute stereochemistry for **7a** was established by converting it into a known compound (see Supporting Information).



This constitutes the first example of highly enantioselective conjugate addition to cinnamates using catalytic amounts of a chiral Lewis acid. Encouraged by the excellent results obtained with *N*-benzylhydroxylamine addition to cinnamates, we then prepared a series of β-aryl-substituted substrates. We wanted to examine electronic effects on substrate selectivity and reactivity. As illustrated in Table 3, pyrrolidinone-derived β-aryl derivatives underwent conjugate addition with *N*-benzylhydroxylamine in good yields and excellent enantioselectivity. The substrate reactivity was largely dependent on the electronic properties of the β-substituent. In general, substrates were more reactive when there was an electron-withdrawing group at the para-position of the benzene ring, and better enantioselectivity was obtained

(13) At 0 °C, reaction times for oxazolidinone cinnamate, pyrrolidinone cinnamate and 3,3-dimethylpyrrolidinone cinnamate were 5, 3, and 6 h, respectively.

(14) Reactions catalyzed by all three Lewis acids were complete in 3 h at 0 °C.

(entries **6c** and **6d**, Table 3). Substrates were less reactive when there was an electron-donating group at the para-position of the benzene ring, and lower enantioselectivity was obtained (entry **6b**). In the case of 3,4-methylenedioxycinnamate, the electron-donating effect at the para-position was compensated with the electron-withdrawing effect at the meta-position, and its reactivity was similar to that of the parent cinnamate (compare entries **6a** and **6g**). When the β-substituents were furyl derivatives, the 3-furyl substrate was much more reactive and selective than the 2-furyl substrate (compare entries **6e** and **6f**). However, both furyl substrates were less reactive than the cinnamates. It is worth noting that the $Mg(ClO_4)_2$ and ligand **2** catalyzed reaction gave better results for substrates with an electron-withdrawing group on the benzene ring. In contrast, the MgI_2 and ligand **2** catalyzed reaction gave better results for substrates with an electron-donating group on the benzene ring.

Control experiments analogous to those reported by Zhao[10] using BnNDOD as the nucleophile and **6a** or **6c** as the substrate suggest that a concerted addition is also operative in our experiments.[15] We have previously proposed a cis-octahedral model for conjugate additions with magnesium Lewis acids and ligand **2**.[4] The sense of stereoinduction in the chemistry presented here is in agreement with this model. Work is in progress to obtain more conclusive evidence for our stereochemical models.

In conclusion, we have shown that *N*-benzylhydroxylamine is more reactive than *O*-benzylhydroxylamine in conjugate addition reactions. Chiral Lewis acid catalyzed *N*-benzylhydroxylamine addition to pyrrolidinone-derived enoates afforded β-aryl-β-amino acid derivatives in high enantiomeric purity. Experiments are underway to apply this methodology in natural product syntheses.

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Supporting Information Available: Experimental procedures and full characterization data for compounds **1**−**7** and details for the establishment of absolute stereochemistry for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The *cis* stereochemistry of the phenyl group and the deuterium (overall *syn* addition) was established by coupling constant analysis.