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Synthesis of β-Substituted α-Amino Acids via Lewis Acid Promoted Enantioselective Radical Conjugate Additions

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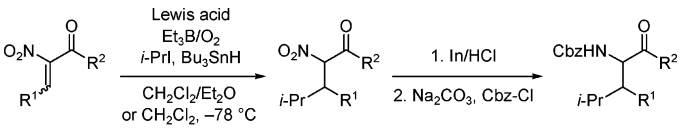

Lewis acid promoted radical conjugate additions to β-substituted α,β-unsaturated α-nitro esters and amides were investigated. With achiral Lewis acids, there was competition between the desired radical conjugate addition and undesired alkene reduction mediated by Bu_3SnH. Zinc Lewis acids provided the greatest amounts of addition products with both substrate classes. Studies with Bu_3SnD indicated that the acidic α-stereocenter of the α-nitro ester products does not racemize under controlled workup conditions. The corresponding α-nitro amides racemized significantly during chromatography, but this problem could be greatly minimized by subjecting the crude adducts to subsequent transformations. Indium-mediated reduction of the nitro group followed by acylation of the resulting amine provided good yields of β-substituted α-amino acid derivatives with mimimal levels of racemization. Attempts to use chiral Lewis acids in a stereoselective variant of this process revealed that Kanemasa's DBFOX/Ph ligand (**14a**) was uniquely effective. Moderate to good ee's and low dr's were obtained with amide substrates. Determination of the absolute configurations of the *syn* and *anti* isomers of adduct **7b** showed that the hydrogen atom abstraction step was significantly more stereoselective than the radical conjugate addition step. A model for substrate binding to the chiral Lewis acid is presented.

Introduction

β-Substituted α-amino acids are present in several peptide natural products;[1] additionally, they are of interest as conformationally constrained analogues of α-amino acids.[2] Accordingly, several methods have been devised for their preparation,[3] including some which involve conjugate additions to α,β-unsaturated amino acid precursors.[3p−t] This strategy is useful for the synthesis of individual amino acids but becomes less practical with complex peptide substrates. The latter compounds contain multiple amides with acidic protons that are incompatible with the basic organometallic reagents typically employed in conjugate additions. However, radical conjugate additions[4] are compatible with unprotected amides. Indeed, additions of nucleophilic radicals to terminally unsubstituted α,β-dehydroamino acid derivatives have been used extensively to construct α-amino acids.[5] Nevertheless, to the best of our knowledge, Renaud's work is the only report of β-substituted α-amino acid synthesis via intermolecular radical conjugate addition to a β-substituted dehydroamino acid.[6]

We reasoned that α,β-unsaturated α-nitro esters and amides would function as extremely reactive acceptors in radical conjugate additions. In fact, we felt that the electrophilicity of these substrates, particularly when complexed to a Lewis acid, would be sufficient to allow additions to β-substituted acceptors to proceed, thereby producing β-substituted α-amino acid derivatives. We disclose herein full details of our investigations into radical conjugate additions of α,β-unsaturated α-nitro esters and amides,[7] including the results of attempts to render this process stereoselective by employing chiral Lewis acids.

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(2) (a) Hruby, V. J. *J. Med. Chem.* **2003**, *46*, 4215. (b) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.

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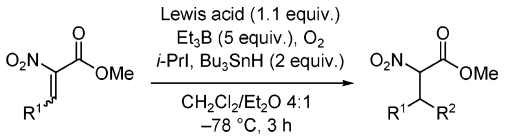
Results and Discussion

To begin our studies, we prepared α,β-unsaturated α-nitro esters **1** via Knoevenagel condensations of methyl nitroacetate with the requisite aldehydes[8] and examined their behavior as acceptors in Lewis acid promoted[9] isopropyl radical conjugate additions (Table 1). We employed conditions developed by Sibi for analogous reactions with α,β-unsaturated *N*-acyloxazolidinone acceptors.[10] Reactions conducted with *p*-methoxyphenyl-substituted nitro ester **1a** revealed that 1,4-reduction of the acceptor by Bu_3SnH[11] was competitive with the desired radical reaction. Use of the Lewis acid $MgBr_2 \cdot OEt_2$ delivered reduced compound **3a** as the sole product. Although we have yet to investigate this issue thoroughly, our observations suggest that reduction of **1a** is at least partially a radical process, as attempts to reduce **1a** in the absence of *i*-PrI returned unreacted starting material.[12] In contrast, Nagano has demonstrated that Bu_3SnH-mediated reductions of aryl acrylates in the presence of $MgBr_2 \cdot OEt_2$ proceed by an ionic mechanism.[13] Accordingly, the reduction of **1a** and related substrates will be the subject of future studies. Fortunately, switching to Zn, Yb, or Cu Lewis acids and increasing the amount of *i*-PrI to 12 equiv resulted in exclusive formation of conjugate addition product **2a**. Radical conjugate addition to **1a** also occurred in the absence of Lewis acid, but larger amounts of *i*-PrI (20 equiv) were required. Phenyl-substituted nitro ester **1b** afforded adduct **2b** with Zn, La, and Sm Lewis acids; curiously, this substrate gave neither **2b** nor **3b** when $MgBr_2 \cdot OEt_2$ or $Yb(OTf)_3$ were used. $ZnCl_2$-promoted additions to *p*-fluorophenyl-substituted nitro ester **1c** were also successful. Interestingly, the $MgBr_2 \cdot OEt_2$-mediated reaction of **1c** produced a minor amount of adduct **2c** along with the expected reduced product **3c**. To date, our attempts to perform radical conjugate additions to isopropyl-substituted nitro ester **1d** have been unsuccessful. The α,β-unsaturated esters were employed as ca. 2:1 mixtures of olefin isomers, and adducts **2** were each isolated in 1:1 dr. Although isomerically pure *Z*-**1a**−**c** could be obtained via recrystallization,[14] use of this material did not improve the dr.

Having established the viability of esters **1a**−**c** as radical conjugate addition acceptors, we wished to examine the performance of the corresponding amides in this reaction. The synthesis of these substrates is detailed in Scheme 1. Direct amide bond formation between

TABLE 1. Radical Conjugate Additions to Esters 1



1a, R^1 = *p*-MeOPh **1c**, R^1 = *p*-FPh **2a–d**, R^2 = *i*-Pr
1b, R^1 = Ph **1d**, R^1 = *i*-Pr **3a–d**, R^2 = H

substrate	Lewis acid	*i*-PrI (equiv)	product	yield[a] (%)
1a	$MgBr_2 \cdot OEt_2$	25	**3a**	60
1a	$ZnCl_2$	5	**3a**	60
1a	$ZnCl_2$	12	**2a**	85
1a	$Zn(OTf)_2$	25	**2a**	85
1a	$Yb(OTf)_3$	5	**3a**	60
1a	$Yb(OTf)_3$	12	**2a**	70
1a	$Cu(OTf)_2$	12	**2a**	80
1a	none	20	**2a**	81
1b	$MgBr_2 \cdot OEt_2$	5	nr[b]	
1b	$ZnCl_2$	5	**2b**	85
1b	$La(OTf)_3$	5	**2b**	58
1b	$Sm(OTf)_3$	5	**2b**	65
1b	$Yb(OTf)_3$	5	nr[b]	
1c	$ZnCl_2$	15	**2c**	85
1c	$MgBr_2 \cdot OEt_2$	15	**2c**,**3c**	7,49
1d	$MgBr_2 \cdot OEt_2$	5	nr[b]	
1d	$ZnCl_2$	5	nr[b]	

[a] For reactions of **1a**, yields were calculated from ^1H NMR due to persistent tin byproducts. All other yields are for isolated materials. [b] Neither product observed.

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(4) For a review, see: Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* Articles in Press (doi:10.1016/j.tet.2005.07.077)

(5) Selected examples: (a) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385. (b) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew Chem., Int. Ed.* **2001**, *40*, 1293. (c) Kabat, M. M. *Tetrahedron Lett.* **2001**, *42*, 7521. (d) Chai, C. L. L.; King, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1173. (e) Axon, J. R.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1995**, 549. (f) Gasanov, R. G.; Il'inskaya, L. V.; Misharin, M. A.; Maleev, V. I.; Raevski, N. I.; Ikonnikov, N. S.; Orlova, S. A.; Kuzmina, N. A.; Belokon,' Y. N. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3343. (g) Kessler, H.; Wittmann, V.; Köck, M.; Kottenhahn, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 902. (h) Crich, D.; Davies, J. W.; Negrón, G.; Quintero, L. *J. Chem. Res., Synop.* **1988**, 140. For a complete listing, see ref 4.

(6) Renaud, P.; Stojanovic, A. *Tetrahedron Lett.* **1996**, *37*, 2569.

(7) Preliminary communication: Srikanth, G. S. C.; Castle, S. L. *Org. Lett.* **2004**, *6*, 449.

(8) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528.

(9) For a review of Lewis acid promoted radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(10) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.

(11) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2585

(12) Treatment of **1a** with $ZnCl_2$ (1.1 equiv) and Bu_3SnH (2 equiv) resulted in recovery of starting material. Repeating this experiment with the addition of Et_3B (5 equiv) also yielded recovered **1a**. When this reaction was conducted in the presence of *i*-PrI (5 equiv), reduced product **3a** was obtained in 60% yield (see the second entry of Table 1).

(13) Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* **2004**, *45*, 2207.

(14) The olefin stereochemistry of *Z*-**1a** and *Z*-**1b** was determined by X-ray crystallography, and the identities of the isomers of **1c** were assigned by comparison of its ^1H NMR spectra to those of **1a** and **1b**. The olefinic proton of the *E*-isomers resonates at 8.1−8.0 ppm, whereas in the *Z*-isomers it resonates at 7.6−7.5 ppm.

SCHEME 1. Synthesis of α,β-Unsaturated α-Nitro Amides 6

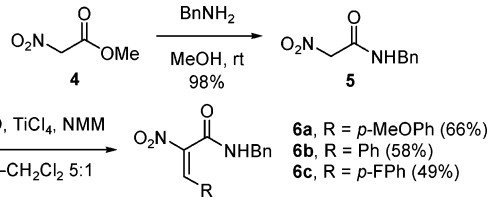
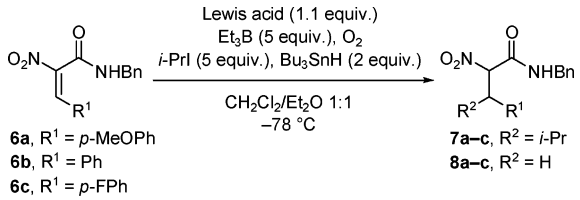


TABLE 2. Radical Conjugate Additions to Amides 6



substrate	Lewis acid	time (h)	7/8	yield[a] (%)
6a	$MgBr_2 \cdot OEt_2$	2	0:100	82
6a	$Zn(OTf)_2$	1	86:14	92
6a	$Cu(OTf)_2$	1	52:48	70
6a	$Yb(OTf)_3$	1	28:72	62
6a	$Sm(OTf)_3$	1	25:75	54 (64)
6a	$La(OTf)_3$	1	25:75	50 (64)
6a	none[b]	4	100:0	72
6b	$Zn(OTf)_2$	3	84:16	84
6b	$Cu(OTf)_2$	3	44:56	52
6b	$Yb(OTf)_3$	3	25:75	58
6c	$Zn(OTf)_2$	4	89:11	80
6c	$Cu(OTf)_2$	4	44:56	46
6c	$Yb(OTf)_3$	4	25:75	30

[a] Sum of the isolated yields of **7** and **8**. Yields in parentheses are based on recovered **6**. [b] 20 equiv of *i*-PrI was used.

methyl nitroacetate (**4**)[15] and benzylamine afforded *N*-benzyl-2-nitroacetamide (**5**). Amide **5** then participated in Knoevenagel condensations with aryl aldehydes, providing α,β-unsaturated α-nitro amides **6** in moderate yields (49−66%). In contrast to esters **1**, the amides were obtained as single alkene diastereomers possessing the *E* configuration.[16]

Our studies of isopropyl radical conjugate additions to amides **6** are summarized in Table 2. We employed the same conditions used in additions to esters **1** with the exception of a change in the CH_2Cl_2/Et_2O ratio from 4:1 to 1:1 in order to facilitate solubility of the substrate-Lewis acid complexes. Additionally, we held the amount of *i*-PrI constant at 5 equiv; greater amounts of this reagent did not lead to alterations in product ratios. In contrast to the additions to esters, the reactions with amide substrates **6** afforded reduced products **8** in varying amounts depending on the Lewis acid. Lanthanide triflate-mediated reactions delivered **8** as the major product, whereas the use of $Cu(OTf)_2$ resulted in roughly equimolar amounts of **7** and **8**. The best results (**7**:**8** = 5−8:1, 80−92% yield) were obtained with $Zn(OTf)_2$ as Lewis acid. As with ester **1a**, a slow radical conjugate addition to **6a** in the absence of Lewis acid was observed which produced **7a** exclusively. However, this process required 20 equiv of *i*-PrI to deliver a reasonable yield of **7a** in 4 h. Comparison of the yields and times of each reaction indicated that *p*-methoxyphenyl-substituted amide **6a** was the best substrate for the radical conjugate addition, followed by phenyl-substituted amide **6b** and *p*-fluorophenyl-substituted amide **6c**. Adducts **7** were isolated as 1:1 mixtures of diastereomers despite the fact that a single olefin isomer of **6** was used in each reaction.

SCHEME 2. Conversion of 2 and 7 into Protected Amino Acids

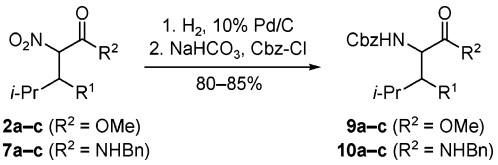
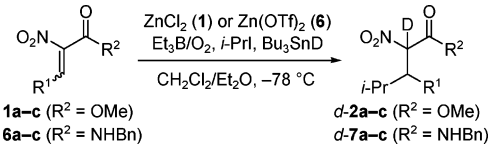


TABLE 3. Incorporation and Retention of Deuterium in 2 and 7



substrate	time (h)	workup	H incorporation[a] (%)
1c	3	H_2O	10
1c	3	0.25 N HCl	4
1b	3	0.25 N HCl	nd[b]
1a	3	0.25 N HCl	nd[b]
6a	1	1 N HCl	4
6b	3	1 N HCl	nd[b]
6c	3	1 N HCl	11

[a] Measured by ^{1}H NMR of *d*-**2a**−**c**- or *d*-**10a**−**c** (see text). [b] Not detected.

Radical conjugate addition products **2** and **7** were successfully converted into *N*-protected amino acid derivatives **9** and **10**, respectively, via catalytic hydrogenation and *N*-Cbz protection (Scheme 2). Thus, we had accomplished our initial goal of synthesizing β-substituted α-amino acids via radical conjugate additions to α,β-unsaturated α-nitro esters and amides. Accordingly, we turned our attention to development of a stereoselective variant of this method. A requirement for such a process is inhibition of racemization of the sensitive α-stereocenters of **2** and **7**.[17] To determine if this would be possible, we performed radical conjugate additions to **1** and **6** with Bu_3SnD. Absence of an α-hydrogen signal in the ^{1}H NMR spectra of *d*-**2** and *d*-**7** would constitute evidence that epimerization could be prevented.

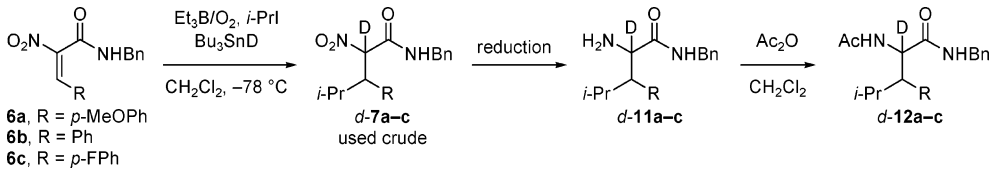
The results of these experiments are contained in Table 3. When we conducted this reaction with electron-poor ester **1c** (R^1 = *p*-FPh), we observed modest levels of α-proton incorporation (10%) when water was used in the workup. Fortunately, when this reaction was worked up with 0.25 N HCl instead of water, the amount of D−H exchange dropped to 4%. Significantly, α-protons were undetectable in the ^{1}H NMR spectra of *d*-**2b** (R = Ph)

(15) Zen, S.; Koyama, M.; Koto, S. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 797.

(16) The *E* olefin stereochemistry of **6a** was determined by X-ray crystallography, and the configurations of **6b** and **6c** were assigned by comparison of their ^{1}H NMR spectra to that of **6a**. The olefinic protons of these compounds resonate at 8.02−8.01 ppm, consistent with the chemical shifts of the corresponding protons in *E*-**1a**−**c**.

(17) The pK_a of ethyl nitroacetate has been measured as 5.62. For a review of the chemistry of α-nitro esters, see: Shipchandler, M. T. *Synthesis* **1979**, 666.

TABLE 4. Nitro Reduction of Amides 7



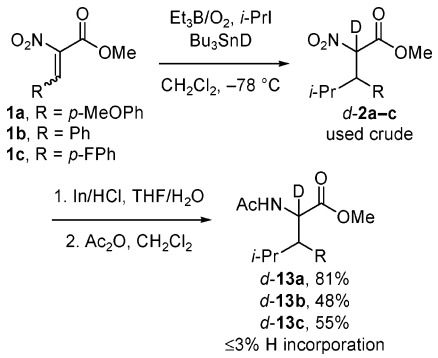
substrate	conditions	*T* (°C)	time (h)	yield[a] (%)	H incorporation (%)
6a	Zn, 6 N HCl, EtOH	rt	12	24	24
6a	Fe, concd HCl, EtOH	80	11	27	17
6a	Sn, concd HCl, EtOH	80	11	49	16
6a	$SnCl_2$, 6 N HCl, EtOH	rt	40	14	10
6a	In, concd HCl, THF/H_2O	rt	12	72	10
6b	In, concd HCl, THF/H_2O	rt	12	71	4
6c	In, concd HCl, THF/H_2O	rt	12	73	4

[a] Isolated yield of *d*-**12** from **6**.

and *d*-**2a** (R = *p*-MeOPh) when this weakly acidic workup was employed. On the other hand, radical conjugate additions to amides **6a**−**c** with Bu_3SnD were characterized by extensive D−H exchange (32−57%, data not shown). NMR spectra implicated the amide hydrogen in this exchange.[18] Moreover, examination of spectra of crude *d*-**7** revealed that loss of the α-deuterium was occurring during SiO_2 chromatography. Consequently, we removed this step from our procedure and subjected crude *d*-**7** to hydrogenation followed by *N*-Cbz protection and chromatography of carbamates **10**. We were pleased to discover that this modification greatly attenuated the D−H exchange, as α-protons were not detected in the ^{1}H NMR spectrum of *d*-**10b** and were observed at low levels (4% and 11%) in the spectra of *d*-**10a** and *d*-**10c**. It is noteworthy that of the six substrates examined in this study, only one exhibited >4% proton incorporation at the α-position.

Although hydrogenating crude amide adducts *d*-**7** allowed us to determine the extent of D−H exchange, the reductions were sluggish and difficult to reproduce due to the presence of tin byproducts and required excess amounts of 10% Pd/C. Therefore, we sought an alternative method that would facilitate high-yielding, reproducible nitro reduction of crude *d*-**7** while keeping α-proton incorporation to a minimum. Our survey of the various methods for nitro group reduction[19] is presented in Table 4. Of the reagents examined, only In/HCl[20] provided acetamides *d*-**12** in good yield with little D−H exchange. These conditions were also applicable to crude adducts *d*-**2** derived from esters **1** (Scheme 3). Accordingly, we selected this reduction protocol for use in our investigations of stereoselective radical conjugate additions to both **6** and **1** due to the fact that chromatographic removal of tin byproducts from the adducts was not required.

SCHEME 3. Indium Reduction of Nitro Esters 2



At this stage, we commenced investigations into stereoselective radical conjugate additions promoted by chiral Lewis acids. We chose α,β-unsaturated α-nitro amide **6a** as our test substrate, and we analyzed each reaction by purifying adduct **7a** and subjecting it to chiral HPLC. From our previous work, we recognized that this survey would be impacted by epimerization of the α-stereocenter. Nevertheless, this assay permitted us to identify promising chiral Lewis acids in rapid fashion. Each reaction was conducted in CH_2Cl_2; ether cosolvents were unnecessary due to the solubilizing effect of the chiral ligands. Unfortunately, most combinations of chiral ligands (bisoxazoline,[21] indan-pybox,[22] prolinol,[23] salen[24]) and Lewis acids (Mg, Zn, Ni, Cu, Al, lanthanides) examined gave both diastereomers of **7a** as racemic mixtures. Moreover, many of the reactions were sluggish and did not proceed to completion, a consequence of replacing small, electron-withdrawing achiral ligands with bulky, electron-rich chiral ligands. Our only promising results came with the DBFOX/Ph ligands developed by Kanemasa and Curran (Figure 1).[25] Use of the parent ligand **14a** with $Mg(NTf_2)_2$[26] afforded **7a** as a 1:1 mixture

(18) ^{1}H NMR spectra recorded immediately after isolation of *d*-**7a**−**c** exhibited amide N−H signals attenuated by an amount consistent with the extent of proton incorporation at the α-position. Over time, the *N*-bound deuterium exchanged with protons derived from adventitious moisture and the amide signals returned to their normal levels of intensity. Attempts to block this exchange by performing radical conjugate additions on protected or tertiary amides were unsuccessful; the *N*-Boc derivative of **6a** afforded reduction product exclusively, whereas *N*-PMB and *N*-Me versions were unreactive.

(19) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 821−828.

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(22) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629.

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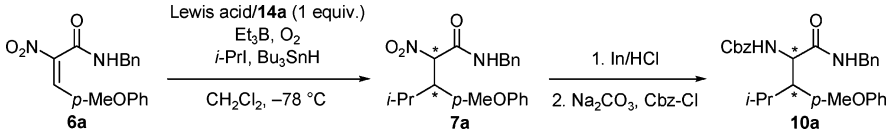
(25) (a) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454. (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (c) Iserloh, U.; Oderaotoshi, Y.; Kanemasa, S.; Curran, D. P. *Org. Synth.* **2003**, *80*, 46.

TABLE 5. Optimization of Stereoselective Radical Conjugate Addition



entry	Lewis acid	Et_3B	concn of **6a** (M)	yield (%)	*syn*/*anti*	% ee (*syn*, *anti*)[a]
1	$MgClO_4$	1.0 M in hexane	0.05	76	2.0:1	19, 13
2	$Mg(NTf_2)_2$	1.0 M in hexane	0.05	44	2.0:1	28, 29
3	$MgClO_4$	3.5 M in CH_2Cl_2	0.05	55	1.5:1	70, 29
4	$Mg(NTf_2)_2$	3.5 M in CH_2Cl_2	0.05	49	1.2:1	77, 72
5	$Mg(NTf_2)_2$[b]	3.5 M in CH_2Cl_2	0.1	76	1.4:1	88, 76
6	$Mg(NTf_2)_2$[c]	3.5 M in CH_2Cl_2	0.1	62	1.2:1	68, 72
7	$Mg(NTf_2)_2$[d]	3.5 M in CH_2Cl_2	0.1	70	1.4:1	84, 64
8	$Mg(NTf_2)_2$[e]	3.5 M in CH_2Cl_2	0.1	57	1.2:1	41, 30

[a] Determined by chiral HPLC (see the Supporting Information for details). [b] Average of two runs. [c] 4 Å MS added. [d] 0.5 equiv of Lewis acid and **14a** was used. [e] 0.3 equiv of Lewis acid and **14a** was used.

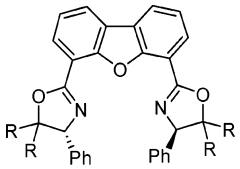
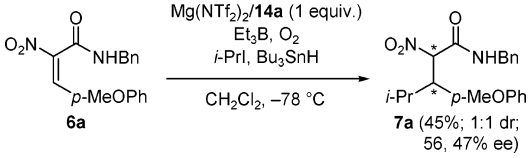


FIGURE 1. DBFOX/Ph ligands.

SCHEME 4. Synthesis of Enantioenriched 7a



of diastereomers in 56 and 47% ee (Scheme 4). Similar results were obtained with $Mg(ClO_4)_2$. Increasing the ligand bulk was detrimental, as Me-DBFOX/Ph (**14b**) delivered **7a** in low ee's (11, 20%), and *n*-Bu-DBFOX/Ph (**14c**) provided racemic products.[27]

Having identified Mg/**14a** as the best chiral Lewis acid, we set out to optimize the reaction conditions and more accurately determine the stereoselectivity. Thus, we isolated and analyzed carbamate **10a** in order to avoid the α-epimerization inherent in purification of **7a**. The results of our investigation of the effects of several parameters on the yield and ee's are summarized in Table 5. All reactions were conducted for 4−5 h with three initiation cycles consisting of addition of Et_3B (5 equiv), *i*-PrI (5 equiv), and Bu_3SnH (2.5 equiv) performed at 1.5 h intervals. The need for extra initiation likely reflects the weaker strength of the chiral Lewis acids relative to their achiral congeners. We discovered that solvent and concentration had a profound effect on the process. When Et_3B was introduced as a 1.0 M solution in hexane, the ee's were low and the concentration of **6a** could not be increased above 0.05 M due to insolubility of the Lewis acid−substrate complex (entries 1 and 2). Switching to a 3.5 M solution of Et_3B in CH_2Cl_2 led to significant increases in ee, with $Mg(NTf_2)_2$ delivering the best results (entries 3 and 4). Elimination of hexane from the reaction mixture allowed us to increase the substrate concentration to 0.1 M, further improving the yield and ee's (entry 5). Addition of 4 Å MS was deleterious to the reaction (entry 6),[28] and substoichiometric quantities of chiral Lewis acid afforded lower ee's (entries 7 and 8). The latter result was attributed to competition from the uncatalyzed radical conjugate addition caused by inefficient turnover of the chiral Lewis acid. Although each diastereomer could be obtained in good ee, the diastereoselectivity was disappointingly low, with only a slight preference observed for the *syn* isomer.[29]

We then proceeded to investigate the substrate scope of the stereoselective reaction using the conditions shown in Table 5, entry 5 (Table 6). Low ee's were observed for all three esters tested (**1a**−**c**) despite the fact that they were used as the pure *Z*-isomers. In contrast, amide substrates **6b** and **6c** delivered protected β-amino acid derivatives **10b** and **10c** with fair ee's. Since the carbonyl groups of amides are generally more electron-rich than those of esters, they may bind more tightly to the chiral Lewis acid, leading to better selectivity.[30] In support of this hypothesis, amide **6a** possessing an electron-rich β-*p*-methoxyphenyl group afforded significantly better ee's than any other substrate tested (Table 5, entry 5). Unfortunately, all of the acceptors examined exhibited only modest (1.4−2.6:1) preferences for the *syn* diastereomer.

In an effort to understand the origins of the stereoselectivity, we converted adducts **7b** into the known amino acids *syn*- and *anti*-**15** (Scheme 5).[29] Measurement of the

(26) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879.

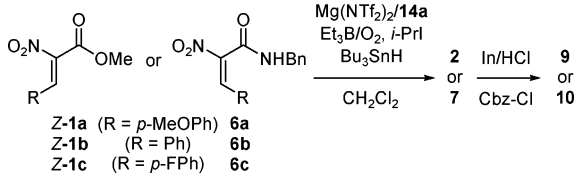
(27) Shirahase, M.; Kanemasa, S.; Hasegawa, M. *Tetrahedron Lett.* **2004**, *45*, 4061.

(28) For a discussion of the effect of molecular sieves on chiral Lewis acids, see ref 23b.

(29) The relative stereochemistry of ester adduct **2b** (see Table 6) was determined by reduction to the amine (In, concd HCl), preparative TLC separation of the diastereomers, and ester hydrolysis (6 N HCl). ^1H NMR spectra of the diastereomers matched the literature data for the known amino acids: Liao, S.; Shenderovich, M. D.; Lin, J.; Hruby, V. J. *Tetrahedron* **1997**, *53*, 16645. Relative stereochemistry assignments of all other adducts are based on comparison of their ^1H NMR spectra to those of **2b**. Specifically, the α- and β-protons of the *syn* isomers each resonated 0.15−0.20 ppm upfield from the corresponding protons of the *anti* isomers, and the *syn*-isopropyl methine resonated ca. 0.20 ppm downfield from the *anti*-isopropyl methine.

(30) In competition experiments, Sato has observed a preference for Lewis acids to complex with acrylamides rather than acrylates: Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576.

TABLE 6. Substrate Scope of Stereoselective Radical Conjugate Addition[a]



substrate	yield (%)	*syn/anti*	% ee (*syn, anti*)[b]
1a	75	2.6:1	21, 28
1b	60	1.7:1	9, 17
1c	66	1.7:1	6, 12
6b	66	1.4:1	64, 62
6c	59	1.6:1	72, 50

[a] For reaction conditions, see Table 5, entry 5. [b] Determined by chiral HPLC of **9**, **10**, or the corresponding acetates **12** (see the Supporting Information for details).

SCHEME 5. Absolute Configuration Determination

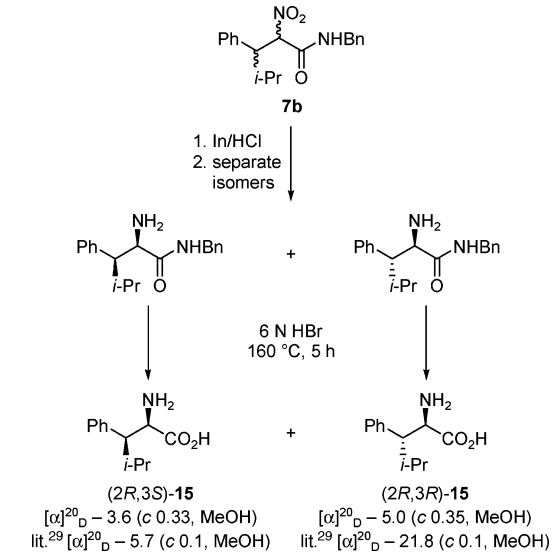


TABLE 7. Selectivity of α and *β* Stereocenter Formation

substrate	α ee (%)	*β* ee (%)
6a	83	20
6b	63	12
6c	64	25

optical rotations of these enantiomerically enriched samples indicated that the major enantiomers possessed the (2*R*,3*S*)- and (2*R*,3*R*)-configurations, respectively. With knowledge of the absolute configurations and relative amounts of all four isomers produced in the chiral Lewis acid mediated radical conjugate addition to amide **6b**, we were able to determine the level of selectivity in formation of the α and *β* stereocenters. By assuming that the absolute configurations of adducts **7a** and **7c** were identical to those of **7b**, we performed analogous calculations for these substrates derived from additions to **6a** and **6c** (Table 7). These data show that the initial alkyl radical addition step is only marginally selective, whereas the subsequent hydrogen atom abstraction proceeds with fair to good stereoselectivity. This suggests that the chiral Lewis acid provides reasonable shielding of the α but not

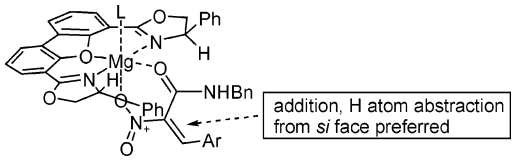
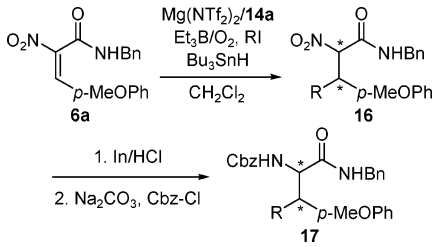


FIGURE 2. Postulated reactive complex.

TABLE 8. Conjugate Additions of Various Alkyl Radicals to 6a



R	yield (%)	*syn/anti*	% ee (*syn*, *anti*)[a]
Et	52	1:1.9	57, 64
c-C_6H_{11}	46	1.4:1	80, 81
t-Bu	*b*		

[a] Determined by chiral HPLC of **17** (*anti* isomer) or the corresponding acetate (*syn* isomer); see the Supporting Information for details. [b] Complex mixture (see text).

the *β* carbon of **6**. The α ee was greatest with *p*-methoxyphenyl-substituted amide **6a**, a fact consistent with our hypothesis that more electron-rich substrates form tighter complexes with the chiral Lewis acid. Finally, the relatively similar ee's obtained for *syn* and *anti* diastereomers (Tables 5 and 6) coupled with the fact that the absolute configuration at the α-carbon is identical for both major enantiomers (Scheme 5) indicates that α-stereocenter formation is under reagent rather than substrate control, an outcome predicted by our preliminary investigations.[7]

Curran and Kanemasa have proposed that enantioselective radical conjugate additions to *N*-enoyloxazolidinones mediated by $Mg(ClO_4)_2$–DBFOX/Ph proceed through an octahedral complex.[25b] This geometry can also explain our stereochemical results (Figure 2). Thus, complexation of the substrate carbonyl oxygen in the plane of the chiral ligand and one of the nitro oxygens perpendicular to this plane leads to shielding of the *re* face of the olefin, with the magnitude of this effect being greatest at the α-carbon. Then, the major product of the reaction is produced by radical conjugate addition and hydrogen atom abstraction occurring on the *si* face of the olefin. This substrate–Lewis acid binding model is purely empirical; it is unclear to us why the amide carbonyl and nitro oxygen would prefer to bind in the orientation shown. Accordingly, this is a subject worthy of future study.

Finally, we performed additions of various alkyl radicals to **6a** in order to more fully determine the scope of the stereoselective radical conjugate addition (Table 8). In comparison to isopropyl radical (Table 5, entry 5), the smaller ethyl radical added to **6a** with lower ee. Interestingly, this addition slightly favored the *anti* diastereomer; the reason for this reversal is unclear. The attenuated ee is also puzzling since the data in Tables 5 and 6 suggest that the *β*-stereocenter has little effect on the

stereochemistry of hydrogen atom abstraction. Additions of cyclohexyl radical proceeded with similar stereoselectivity but lower yields than those of isopropyl radical. However, no adducts could be obtained with *tert*-butyl radical despite the use of excess reagents (a total of 30 equiv of *t*-BuI, 30 equiv of Et_3B, and 15 equiv of *n*-Bu_3SnH added in six portions). Acceptor **6a** was completely consumed, and no reduction product could be detected, suggesting that addition of the bulky tertiary radical to the substituted β-carbon is slower than polymerization of the alkene or other decomposition pathways. Consequently, it appears that the stereoselective reaction performs best with secondary alkyl radicals. Nevertheless, a more extensive study of additions of various nucleophilic radicals to **6a** is required in order to better understand the scope and limitations of this process.

Conclusions

We have demonstrated that α,β-unsaturated α-nitro esters and amides undergo Lewis acid promoted radical conjugate additions, affording β-substituted α-amino acid derivatives. With achiral Lewis acids, competitive reduction is more pronounced with amides, presumably due to stronger substrate−Lewis acid complexes. Nevertheless, good yields of adducts can be obtained from both classes of acceptors when Zn Lewis acids are employed. Through the use of Bu_3SnD, we discovered a workup, nitro reduction, and isolation protocol that greatly minimizes epimerization of the extremely acidic α-stereocenter present in adducts **2** and **7**. This finding led us to survey several chiral Lewis acids in an attempt to develop a stereoselective process. The best chiral promoter examined to date is Kanemasa's DBFOX/Ph ligand (**14a**) combined with $Mg(NTf_2)_2$ or $Mg(ClO_4)_2$. This complex affords protected amino acid derivatives **10** with fair to good ee's but disappointingly low dr's. Determination of the absolute configuration of the major enantiomers produced in additions to **6b** revealed that hydrogen atom abstraction proceeds with significantly better selectivity than does the radical addition. Accordingly, a chiral Lewis acid capable of providing improved enantiofacial discrimination at the acceptor β-carbon is necessary to render these stereoselective radical conjugate additions practical.

Although the additions controlled by chiral Lewis acids require further development, the corresponding reactions with achiral Lewis acids have great potential in peptide synthesis. The utility of amides **6** as acceptors suggests that peptides containing the α,β-unsaturated α-nitro amide moiety may also be good substrates for this reaction. The stereochemical information present in these acceptors could provide the necessary stereocontrol. Moreover, the ability to selectively epimerize the α-nitro amide stereocenter and obtain a thermodynamically more stable product would be extremely useful provided a means of controlling the radical addition step could be devised. Efforts along these lines in the context of natural products total synthesis are underway and will be reported in due course.

Experimental Section

General Procedure for Radical Conjugate Additions to Esters 1a−c Promoted by Achiral Lewis Acids. To a solution of **1** (0.12 mmol) in CH_2Cl_2−Et_2O (4:1, 1 mL) was added a Lewis acid (0.14 mmol). The resultant mixture was stirred at rt for 30 min. The clear solution was cooled to −78 °C and treated first with *i*-PrI (71 μL, 106 mg, 0.63 mmol), then immediately with Et_3B (1.0 M solution in hexanes, 0.66 mL, 0.63 mmol), and finally with Bu_3SnH (77 μL, 81 mg, 0.25 mmol). O_2 was added via syringe (2 mL) every 30 min, and the reaction was stirred at −78 °C for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) followed by 0.25 N HCl (5 mL), and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 12 cm, 0−0.75% EtOAc in hexanes gradient elution) afforded the adducts as colorless oils (**2a**−**c**) or the reduced compounds (**3a**, **3c**) along with tin impurities. Analytically pure samples were prepared by subjecting the compounds to further chromatography (same conditions).

Methyl 3-(4-Methoxyphenyl)-4-methyl-2-nitropentanoate (2a). Prepared with $ZnCl_2$ or $Zn(OTf)_2$ as Lewis acid and obtained in 85% yield as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 and 7.13 (2d, J = 9.0 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.60 and 5.56 (2d, J = 10.5 and 11 Hz, 1H), 3.85 and 3.79 (2s, 3H), 3.78 and 3.52 (2s, 3H), 3.62−3.54 (m, 1H), 2.10−2.02 (m, 1H), 0.92−0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8 and 164.0, 159.2, 132.5, 130.8, 130.4, 127.0 and 126.8, 113.9, 91.2 and 90.8, 55.4, 53.8 and 53.4, 51.8, 29.5 and 29.4, 21.7 and 21.2, 18.1 and 18.0; IR (film) ν_{max} 3240, 1656, 1545 cm^{-1}; HRMS (EI) *m/z* 281.1256 (M^+, $C_{14}H_{19}NO_5$ requires 281.1263).

Methyl 2-Deuterio-3-(4-methoxyphenyl)-4-methyl-2-nitropentanoate (*d*-2a). ^{1}H NMR ($CDCl_3$, 500 MHz) was identical to **2a** except for the absence of the two doublets at δ 5.60 and 5.56. Also, the multiplet at δ 3.62−3.54 appeared as two doublets centered at δ 3.60 and 3.56 (J = 6.5 Hz).

Methyl 4-Methyl-2-nitro-3-phenylpentanoate (2b). Prepared with $ZnCl_2$ as Lewis acid and obtained in 85% yield as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.30 (m, 3H), 7.18−7.11 (m, 2H), 5.66 and 5.62 (2d, J = 11 and 10.5 Hz, 1H), 3.93 and 3.54 (2s, 3H), 3.68−3.59 (m, 1H), 2.06−2.00 (m, 1H), 0.86 and 0.79 (2d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7 and 163.9, 135.2 and 135.1, 132.7 and 132.5, 130.6 and 130.0, 129.7 and 129.6, 129.3 and 129.0, 128.4 and 127.9, 91.0 and 90.8, 53.8 and 53.6, 52.5 and 52.4, 29.6 and 29.4, 21.7 and 21.1, 18.1 and 18.0; IR (film) ν_{max} 3242, 1651, 1555 cm^{-1}; HRMS (FAB) *m/z* 274.1054 (MNa^+, $C_{13}H_{17}NO_4Na$ requires 274.1055).

Methyl 2-Deuterio-4-methyl-2-nitro-3-phenylpentanoate (*d*-2b). ^{1}H NMR ($CDCl_3$, 500 MHz) was identical to **2b** except for the absence of the two doublets at δ 5.66 and 5.62. Also the multiplet at δ 3.68−3.59 appeared as two doublets centered at δ 3.66 and 3.61 (J = 8.5 Hz).

General Procedure for Radical Conjugate Additions to Amides 6a−c Promoted by Achiral Lewis Acids. To a solution of **6** (0.080 mmol) in CH_2Cl_2−THF (1:1, 1.5 mL) was added a Lewis acid (0.088 mmol). The resultant mixture was stirred at rt for 30 min. The clear solution was cooled to −78 °C and treated with first with *i*-PrI (47 μL, 68 mg, 0.40 mmol), then immediately with Et_3B (1.0 M solution in hexanes, 0.41 mL, 0.40 mmol), and finally with Bu_3SnH (50 μL, 52 mg, 0.17 mmol). O_2 was added via syringe (2 mL) every 30 min, and the reaction was stirred at −78 °C for 1−4 h. The mixture was diluted with CH_2Cl_2 (15 mL) followed by 1 N HCl (5 mL), and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 12 cm, 2−8% EtOAc in hexanes gradient elution) afforded mixtures of **7** and **8** as white solids. Analytically pure samples of **7a**−**c** were prepared by washing the solid with cold hexanes.

***N*-Benzyl-3-(4-methoxyphenyl)-4-methyl-2-nitropentanamide (7a).** Prepared with $Zn(OTf)_2$ as Lewis acid, obtained as an 86:14 mixture with **8a** in 82% combined yield, and isolated as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.28 (m, 2H), 7.26−7.18 (m, 3H), 7.02 (d, J = 8.5 Hz, 2H), 6.87 and 6.40 (2br s, 1H), 6.80 (d, J

= 8.5 Hz, 2H), 5.59 and 5.57 (2d, J = 10.0 and 10.5 Hz, 1H), 4.46 and 4.20 (dd and d, J = 5.5, 15 Hz and 6.0 Hz, 1H), 4.45 and 4.20 (dd and d, J = 6.0, 12.5 Hz and 6.0 Hz, 1H), 3.81 and 3.77 (2s, 3H), 3.50 and 3.44 (2dd, J = 5.0, 11 Hz and 5.0, 10.0 Hz, 1H), 2.08−2.00 and 1.98−1.92 (2m, 1H), 0.94 and 0.90 (2d, J = 8.0 Hz, 3H), 0.91 (d, J = 8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9 and 162.2, 159.4, 137.0 and 136.9, 130.9 and 130.3, 129.1 and 128.8 (2C), 128.1, 127.9 and 127.85 (2C), 127.80 (2C), 126.8 and 126.2, 114.0 and 113.9, 93.1 and 92.9, 55.4, 54.0 and 53.3, 44.2 and 44.0, 29.5 and 28.9, 21.8 and 21.3, 18.2 and 17.6; IR (film) ν_{max} 3259, 1659, 1552 cm^{-1}; HRMS (FAB) *m/z* 379.1647 (MNa^+, $C_{20}H_{24}N_2O_4Na$ requires 379.1634).

***N*-Benzyl-4-methyl-2-nitro-3-phenylpentanamide (7b).** Prepared with $Zn(OTf)_2$ as Lewis acid, obtained as an 84:16 mixture with **8b** in 84% combined yield, and isolated as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.24 (m, 6H), 7.20 (d, J = 10.5 Hz, 2H), 7.10 and 6.79 (2d, J = 7.0 and 8.0 Hz, 2H), 6.85 and 6.37 (2br s, 1H), 5.64 and 5.62 (2d, J = 7.5 and 10.5 Hz, 1H), 4.51−4.41 (m, 1H), 4.25−4.15 (m, 1H), 3.57−3.50 (m, 1H), 2.12−2.04 and 2.03−1.97 (2m, 1H), 0.98−0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.8 and 162.1, 137.0 and 136.8, 134.9 and 134.5, 129.9 and 129.3, 129.1 and 128.8 (2C), 128.7, 128.6 and 128.5 (2C), 128.18 and 128.10, 127.9 and 127.7, 128.0 and 127.8 (2C), 93.0 and 92.8, 54.4 and 54.0, 44.3 and 44.0, 29.5 and 28.9, 21.8 and 21.3, 18.1 and 17.7; IR (film) ν_{max} 3221, 1650, 1564 cm^{-1}; HRMS (FAB) *m/z* 327.1704 (MH^+, $C_{19}H_{22}N_2O_3H$ requires 327.1709).

General Procedure for Radical Conjugate Additions Promoted by Chiral Lewis Acid. A solution of $Mg(NTf_2)_2$ (116.9 mg, 0.20 mmol) and ligand **14a** (91.7 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was stirred at rt for 1−2 h and then treated with *Z*-**1** or *E*-**6** (0.20 mmol). The walls of the reaction vessel were washed with CH_2Cl_2 (0.5 mL), and the mixture was stirred at −78 °C for 30 min. Alkyl iodide (1.0 mmol), Bu_3SnH (134 μL, 145 mg, 0.50 mmol), Et_3B (3.45 M solution in CH_2Cl_2, 290 μL, 1.0 mmol), and O_2 (10 mL) were added sequentially, and identical quantities of these reagents were added twice more at 1.5 h intervals. The mixture was stirred at −78 °C for an additional 1.5 h (4.5 h total since initiation of radical reaction), treated with 2 N HCl (10 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were concentrated in vacuo.

The crude adduct **2** or **7** was treated with concd HCl (0.60 mL, 7.2 mmol), H_2O (3 mL), THF (3 mL), and indium powder (184 mg, 1.6 mmol). The resulting mixture was stirred at rt for 12 h, the solids were removed, and the volatiles were removed in vacuo. The residue was diluted with 1 N HCl (10 mL), and tin byproducts were removed by extraction with hexanes (3 × 10 mL). The aqueous layer was treated with Na_2CO_3 (added until pH ≈ 8) and satd aq sodium potassium tartrate solution (10 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Thirty percent of the crude amine mixture was subjected to flash chromatography (SiO_2, 25−60% EtOAc in hexanes gradient elution for amines derived from **2** or 1−4% MeOH in CH_2Cl_2 gradient elution for amines derived from **7**) to afford samples of the pure *syn* and *anti* diastereomers suitable for chiral HPLC analysis after further derivatization.

The remaining 70% of the crude amine mixture was treated with benzyl chloroformate (22.8 μL, 27.6 mg, 0.15 mmol), Na_2CO_3 (16.3 mg, 0.15 mmol), and THF (3 mL). The resulting mixture was stirred at rt for 12 h, concentrated in vacuo, and purified by flash chromatograghy (SiO_2, 7−13% EtOAc in hexanes gradient elution for carbamates derived from **2** or 20−30% EtOAc in hexanes gradient elution for carbamates derived from **7**), affording carbamates **9** or **10** as white solids that were mixtures of diastereomers.

Methyl 2-benzyloxycarbonylamino-3-(4-methoxyphenyl)-4-methylpentanoate (9a) (75% yield, 2.6:1 *syn*/*anti*): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.34 (m, 5H), 6.98 and 6.94 (2d, J = 9.0 and 8.5 Hz, 2H), 6.84−6.81 (m, 2H), 5.14 and 5.11 (s, 2H), 5.00 (br s, 1H), 4.99 and 4.84 (2d, J = 6 and 9.5 Hz, 1H), 4.86 and 4.82 (2dd, J = 6.5, 9.0 Hz, 1H), 3.78 (s, 3H), 3.65 and 3.63 (2s, 3H), 2.84−2.79 and 2.62−2.58 (2m, 1H), 2.26−2.20 and 2.09−2.02 (2m, 1H), 1.26−1.19 and 0.79−0.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7 and 171.7, 158.9, 156.8 and 155.9, 136.5 and 136.4, 130.5, 130.1 (2C), 129.7 (2C), 128.8 and 128.7, 128.4 and 128.3 (2C), 127.9 and 127.2, 114.2 and 113.9, 67.3 and 67.1, 56.2 and 56.0, 55.3, 54.5, 52.3 and 52.1, 29.9 and 29.0, 21.5, 21.1; IR (film) ν_{max} 3346, 2959, 1726, 1602, 1222, 1048 cm^{-1}; HRMS (FAB) *m/z* 386.1975 (MH^+, $C_{22}H_{27}NO_5H$ requires 386.1967).

s*yn*-**9a** was obtained in 21% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane/*i*-PrOH, 1 mL/min; t_R = 16.9 min (major), 27.3 min). *anti*-**9a** was obtained in 28% ee, as analyzed by HPLC under identical conditions (t_R = 11.4 min (major), 25.2 min).

Methyl 2-Benzyloxycarbonylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanoate (*d*-9a). (Produced by combination of the general procedure for radical conjugate additions to esters promoted by achiral Lewis acids with the reduction and protection protocols contained in the chiral Lewis acid general procedure.) ^{1}H NMR ($CDCl_3$, 500 MHz) was identical to **9a** except for the absence of the two signals at δ 4.99 and 4.84. Also, the multiplets at δ 2.84−2.79 and 2.62−2.58 appeared as two doublets centered at δ 2.82 and 2.61 (J = 10.0 and 10.5 Hz). HRMS (FAB) *m/z* 387.2018 (M^+, $C_{22}H_{26}DNO_5H$ requires 387.2012).

***N*-Benzyl 2-benzyloxycarbonylamino-3-(4-methoxyphenyl)-4-methylpentanamide (10a)** (76% yield, 1.4:1 *syn*/*anti*): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.24 (m, 7H), 7.17 (d, J = 10.5 Hz, 2H), 7.05 (dd, J = 8.5, 14.5 Hz, 2H), 6.81−6.73 (m, 3H), 6.25 and 6.01 (2 br s, 1H) 5.35 and 4.97 (2d, J = 7.0 and 5.5 Hz, 1H), 5.12 and 5.09 (2s, 2H), 4.72 and 4.61 (2t, J = 4.5 and 9.5 Hz, 1H), 4.45−4.24 and 4.37 (m and dd, J = 7.0, 15.5 Hz, 1H), 4.03 (dd, J = 4.5, 15.5 Hz, 1H), 3.87 (s, 3H), 3.19−3.08 and 2.87−2.77 (2m, 1H), 2.38−2.22 and 2.10−1.94 (2m, 1H), 1.05 and 0.91 (2d, J = 6.0 Hz, 3H), 0.80 and 0.77 (2d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 159.4, 156.3, 138.4 and 137.5, 136.3 (2C), 129.8, 128.79 and 128.72 (2C), 128.5 (2C), 128.4, 128.36, 128.32 (2C), 127.8, 127.6, 127.4 and 127.3 (2C), 113.7, 67.4, 57.2, 55.7 and 55.6, 54.8 and 53.4, 43.5, 28.5, 21.7, 18.7; IR (film) ν_{max} 3281, 2930, 1649, 1520 cm^{-1}; HRMS (FAB) *m/z* 483.2252 (MNa^+, $C_{28}H_{32}N_2O_4Na$ requires 483.2260).

syn-**10a** was obtained in 88% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane/*i*-PrOH, 1 mL/min; t_R = 20.3 min (major), 27.8 min). *anti*-**10a** was obtained in 76% ee, as analyzed by HPLC under identical conditions (t_R = 27.6 min (major), 38.4 min).

***N*-Benzyl 2-Benzyloxycarbonylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanamide (*d*-10a).** (Produced by combination of the General Procedure for radical conjugate additions to amides promoted by achiral Lewis acids with the reduction and protection protocols contained in the chiral Lewis acid general procedure.) ^{1}H NMR ($CDCl_3$, 500 MHz) was identical to **10a** except for the absence of the signals at δ 4.72 and 4.61. Also, the two multiplets at δ 3.19−3.08 and 2.87−2.77 appeared as two doublets centered at δ 3.11 and 2.80 (J = 8.5 and 9.0 Hz). HRMS (FAB) *m/z* 484.2308 (MNa^+, $C_{28}H_{31}DN_2O_4Na$ requires 484.2322).

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Supporting Information Available: General experimental details, synthetic procedures, spectral data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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