Asymmetric Synthesis of β-Amino Acid Derivatives via Catalytic Conjugate Addition of Hydrazoic Acid to Unsaturated Imides

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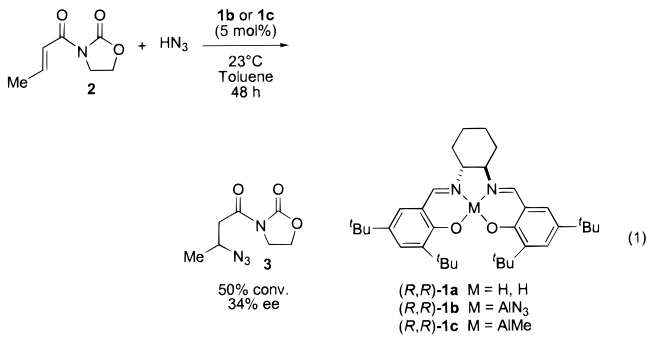
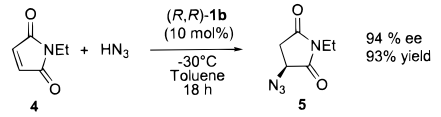
Interest in synthetic routes to β-amino acids can be traced to the presence of these building blocks in a variety of biologically-interesting natural products,[1] and to the recent revelation that derived peptides show well-defined secondary structures.[2] While several methods for the construction of enantiomerically enriched β-amino acid derivatives have been developed utilizing either chiral substrates or chiral auxiliaries,[1a,3] the enantioselective catalytic synthesis of these targets from achiral precursors remains a significant challenge.[4] The conjugate addition of amines or their synthetic equivalents to α,β-unsaturated carbonyl compounds constitutes one of the most direct and attractive strategies for the construction of β-amino acid derivatives.[4a,c] In this paper, we describe a significant advance in this direction, with the highly enantioselective conjugate addition of hydrazoic acid (HN_3) to α,β-unsaturated imides catalyzed by a readily available chiral (salen)Al(III) complex.

Metal complexes of the salen ligand **1a** have been shown to be effective for a wide variety of asymmetric nucleophile−electrophile reactions, including the opening of epoxides by azide,[5] water,[6] carboxylic acids,[7] and phenols,[8] the addition of HCN to imines,[9] and hetero-Diels−Alder reactions between electron-rich dienes and aldehydes.[10] In a preliminary screen of conjugate addition reactions using nitrogen-based nucleophiles, we evaluated this chiral template for catalysis of the addition of hydrazoic acid[11] to oxazolidinone **2** (eq 1). The best results were obtained with aluminum azide complex **1b**, which afforded the azide adduct **3** in 34% ee and 50% conversion after 48 h.[12] Although complex **1b** displayed irreproducible activity after prolonged storage, it could be generated conveniently *in situ* from the salen ligand **1a** and diethylaluminum azide;[13] alternatively, the shelf-stable (salen)Al(III)Me complex **1c** could be employed as precatalyst. Complex **1c** undergoes rapid conversion to azide complex **1b** under the conditions of catalysis, and identical results were obtained in reactions employing either of the two complexes.



(1)

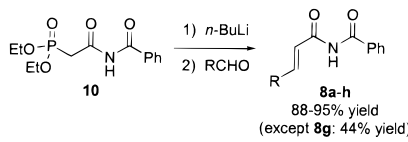
Pursuant to this encouraging preliminary result, we evaluated a wide variety of easily accessible conjugate acceptors for the addition of HN_3 catalyzed by **1b**. Of these, *N*-alkylmaleimides displayed both excellent reactivity and enantioselectivity in the conjugate addition reaction. Under optimal conditions, *N*-ethylmaleimide (**4**) underwent clean conversion to afford the azide adduct **5** in 94% ee and 93% yield (eq 2).



(2)

It appeared that the imide group common to **2** and maleimide **4** was critical for effective catalytic conjugate addition of HN_3 in the presence of the (salen)Al catalyst. On that basis, we examined a series of acyclic α,β-unsaturated imides as potential substrates (Table 1). Imide **6** displayed a higher level of reactivity than oxazolidinone **2**, undergoing complete conversion within 6 h at ambient temperature; however, only modest (31%) enantioselectivity was obtained. The unsubstituted imides **7** and **8a** were equally reactive, but afforded substantially higher enantioselectivity (60−68% ee at rt). Reducing the reaction temperature to −40 °C led to formation of the azide adduct **9a** in excellent yield and enantioselectivity (96% yield, 96% ee).

Encouraged by the excellent results obtained with the *N*-benzoyl imide derivative **8a**, we prepared a series of analogs (**8b**−**h**) varying in the identity of the β-substituent. These imide derivatives were prepared conveniently in a single step via a Horner−Emmons reaction of the appropriate aldehyde with phosphonate **10** (eq 3). This modular approach allowed rapid access to a wide variety of unsaturated imides in high yield, and appeared to be limited only by the availability of the requisite aldehyde.



(3)

As illustrated in Table 2, imides **8a**−**g** underwent conjugate addition of HN_3 in the presence of catalyst **1c** in excellent yield

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(12) Of the complexes screened under these conditions (5 mol % catalyst, rt, 48 h), only the corresponding (salen)Al(III) chloride (31% conversion, 28% ee), (salen)Cr(III) azide (23% conversion, 9% ee), and (salen)Ru(III) chloride (46% conversion, 4% ee) proved catalytically active.

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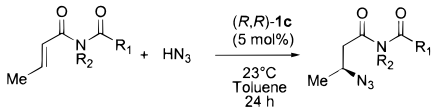
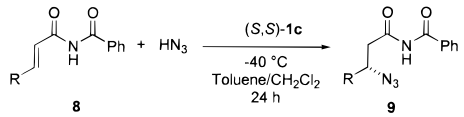
Table 1. Asymmetric Conjugate Addition of HN_3 to Imides **6**−**8a** Catalyzed by (*R*,*R*)-**1c**



	R1	R2	ee (%)[a]	conv (%)
6	Me	Me	31	100
7	Me	H	62	100
8a	Ph	H	68	100

[a] Full experimental details and ee analyses are provided in the Supporting Information.

Table 2. Conjugate Addition of HN_3 to Unsaturated Imides **8a**−**h** Catalyzed by (*S*,*S*)-**1c**[a]



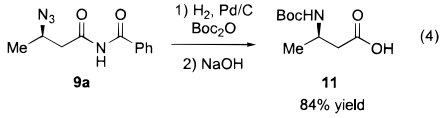
	R	ee (%)[d]	yield (%)[e]		R	ee (%)[d]	yield (%)[e]
8a	Me	96	96	**8e**	*t*-Bu[b]	97	99
8b	Et	97	97	**8f**	Bn	95	97
8c	*n*-Pr	95	97	**8g**	CH_2OBn	96	93
8d	*i*-Pr	97	98	**8h**	Ph[c]	58	60

[a] Unless noted otherwise, reactions were carried out on a 0.5 mmol scale at −40 °C with 5 mol % catalyst and 6.6 equiv of HN_3. [b] −30 °C. [c] 23 °C, 10 mol % catalyst. [d] Enantiomeric excesses were measured by chiral HPLC on a Pirkle L-leucine column (Regis). The absolute stereochemistry of **9a** was established by conversion to the known *N*-Boc amino acid **11**. All other assignments were made by analogy. [e] Isolated yield after silica gel chromatography.

and ee. The reaction was largely insensitive to the steric properties of the β-substituent, with alkyl groups ranging from methyl to *tert*-butyl all providing products in 95−97% ee.[11] However, the rate of the reaction was somewhat lower for **8e** (R = *tert*-butyl), and a slightly higher temperature was required to achieve complete conversion. The benzyl ether-containing substrate **8g** underwent clean reaction as well, suggesting that a fair level of tolerance toward Lewis basic functionalities is to be anticipated for this reaction. Cinnamate derivative **8h** was considerably less reactive than the alkyl-substituted substrates, undergoing incomplete conversion after 24 h at room temperature. It is worth noting that the ee of the product was similar to that obtained with **8a** under the same conditions, suggesting that the problem for this important substrate subclass is one of reactivity and not enantioselectivity.

In preliminary kinetic studies, it has been established that the rate of the conjugate addition reaction displays a first-order dependence on catalyst **1b**. This stands in contrast to the enantioselective addition of azide to epoxides catalyzed by the chromium analog of **1b**, which displays a second-order dependence on the metal complex.[14] In the latter case, a dual role for the catalyst is indicated wherein the chiral chromium complex serves both as a Lewis acid activator of electrophile and as a nucleophile-delivery agent. The kinetic data obtained in the reactions of **1b** suggest that the aluminum catalyst is fulfilling only one of those functions—either as Lewis acid *or* as mediator of azide transfer—in the conjugate addition to unsaturated imides.[15]

The utility of β-azido imide adducts **9** as precursors to β-amino acid derivatives was illustrated through the transformation of azide **9a** into *N*-Boc-β-aminobutyric acid[16] (eq 4). The azide group of



(4)

9a was hydrogenated and protected as the *tert*-butyl carbamate **11** in one operation in 90% yield.[17] The imide group underwent regioselective cleavage with aqueous sodium hydroxide to provide *N*-Boc-protected carboxylic acid **12** in 84% yield.

There are several interesting implications to the finding that (salen)Al complexes are effective catalysts for the enantioselective addition of azide to unsaturated imides. The reaction itself employs an inexpensive and easily accessed catalyst, and it involves a simple experimental protocol. Coupled with the straightforward reduction and hydrolysis of the β-azido imide products, this constitutes a useful and general method for the synthesis of highly enantioenriched β-amino acids. In addition, unsaturated imides such as **6**−**8** are easily accessible but have rarely been used in organic synthesis. Their utility in the conjugate addition chemistry suggests that they may be interesting substrates for other asymmetric catalytic reactions. Finally, the results summarized here constitute the first example of highly enantioselective 1,4-addition catalyzed by chiral (salen)metal complexes,[4d] and therefore they expand the chemistry of these versatile catalyst systems to an important new reaction class. The full scope of this conjugate addition chemistry remains to be established.

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Supporting Information Available: Complete experimental procedures, analytical data, and chiral chromatographic analyses of racemic and enantiomerically enriched conjugate addition products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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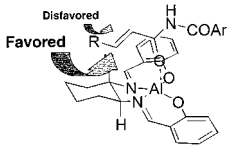
(15) The similarly high enantioselectivities obtained with maleimide **4** and acyclic substrates **8a**−**g** suggest a reactive s-trans conformation of the unsaturated imide in the conjugate addition reaction. If a Lewis acid mode of activation involving one-point binding is assumed, a simplified stereochemical model can be devised, such as the one below, that accounts for the observed facial selectivity.



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