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Enantioselective Formal Hydration of α,β-Unsaturated Imides by Al-Catalyzed Conjugate Addition of Oxime Nucleophiles

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The conjugate addition of oxygen-centered nucleophiles to electron-deficient olefins has proven a challenging problem in organic synthesis. The relative weakness of *O*-nucleophiles, coupled with problems associated with reaction reversibility, has hampered the development of general methods for this transformation.[1] As a result, stereoselective variants of this reaction have been limited to diastereoselective *O*-conjugate addition reactions of chiral alkoxides to highly activated acceptors,[2] intramolecular hemiacetal alkoxide conjugate additions,[3] and a single example of a catalytic asymmetric ring-closure process involving a phenol.[4] In this communication, we describe the development of the catalytic asymmetric oxygen-centered addition of salicylaldoxime to α,β-unsaturated imides, a process that enables the synthesis of β-hydroxy carboxylic acid derivatives with high levels of enantioselectivity.[5]

Over the past several years, our laboratory has demonstrated the utility of (salen)aluminum complexes (**1a**−**c**, Figure 1) as catalysts for the highly enantioselective conjugate addition of a variety of weakly acidic[6] nucleophiles (HN_3,[7a] HCN,[7b] malononitrile and substituted cyanoacetates[7c]). In the hopes of using this catalyst system to induce the conjugate addition of oxygen-centered nucleophiles, we sought reagents with increased acidity and nucleophilicity relative to typical alcohols. Oximes fit both of these criteria,[8] and the oxime ethers that would result from such conjugate additions contain a potentially labile *N*−*O* bond, enabling a reductive cleavage to afford formal hydration products (Scheme 1).

Many readily available oximes were screened with catalysts **1b** and **1c** in a variety of solvents,[9] and inexpensive salicylaldoxime (**3**)[10] emerged as the *O*-centered nucleophile of choice. Under optimized conditions, μ-oxo dimer catalyst [(*R*,*R*)-(salen)Al]$_2$O (**1c**)[7c] effected the addition of salicylaldoxime to a variety of α,β-unsaturated imides (**2a**−**f**) in cyclohexane (Table 1). These additions proceeded efficiently (≥90% conversion) with excellent enantioselectivities (≥97% ee) using 5 mol % of the dimeric catalyst. Hydrogenolysis of the crude oxime ethers afforded the formal hydration products **4a**−**f** in high overall yields without erosion of optical purity.

As highlighted in Table 1 (products **4d**−**f**), the method is tolerant of ester, acetal, and silyl ether functionality, allowing its potential application as an acetate aldol alternative in polyketide natural product synthesis (see below). Practical limitations include prohibitively slow rates with substrates bearing aromatic or highly hindered β-substituents, an apparent necessity for partial solubility of the substrate in the alkane-based reaction media, and incompatibility of functional groups reducible under the hydrogenolysis conditions.[11]

To assess the potential applicability of this method to the synthesis of polyproprionate or polyacetate natural products, we evaluated the ability of catalyst **1c** to deliver stereochemically complex products with high levels of catalyst-induced diastereoselectivity. Substrates **5**, **7**, and **9** were prepared in enantioenriched form and subjected to the two-step formal hydration sequence (see Scheme 2).

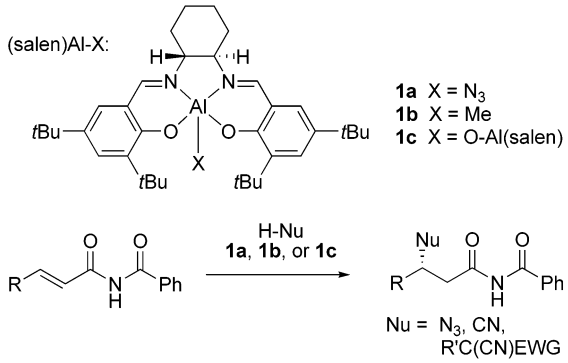
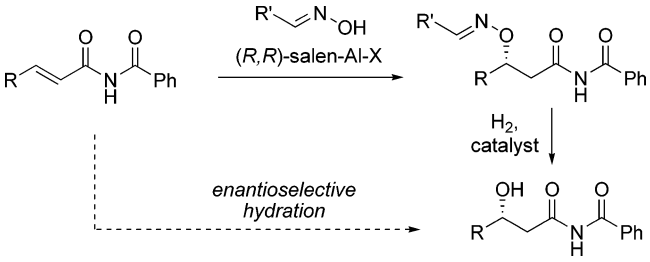


Figure 1. (salen)Al-Catalyzed asymmetric conjugate additions to α,β-unsaturated imides.

Scheme 1. Approach to the Enantioselective Hydration of α,β-Unsaturated Imides by an Asymmetric Conjugate Oxime Addition/Hydrogenolysis Sequence



High conversions were attained in the oxime additions, with nearly complete catalyst control. Thus, reaction of ethyl (*R*)-3-hydroxybutyrate-derived **5** in the presence of *(R,R)*-**1c** led to highly selective formation of the 1,3-*anti* addition product **6a**, and *(S,S)*-**1c** delivered the 1,3-*syn* product **6b**. Analogous results were obtained with malic acid-derived substrate **7** and Roche ester-derived imide **9**.[12] All products were isolated in good yields after hydrogenolysis of the crude oxime ethers.[13] The utility of this approach is envisioned to be greatest in complex settings when substrate-controlled aldol reactions fail to provide acceptable levels of stereochemical control.

The imide functionality required for achieving high enantioselectivity in these (salen)Al-catalyzed conjugate addition reactions[7a] is converted readily into a variety of other carboxylic acid derivatives. For example, ethanolysis of the β-hydroxy imides was catalyzed by Er(OTf)$_3$ with excellent regioselectivity and in high yields;[7c,14] the mild conditions were compatible with ester and acetal functionalities such as those in the imide products derived from **4d** and **4e**.[15] This process enabled the verification of the absolute stereochemistry of the formal hydration products, as the ester

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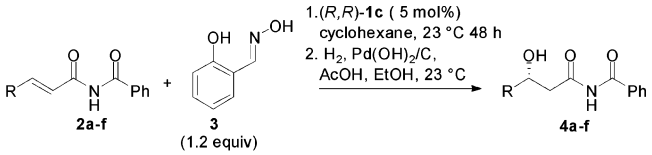
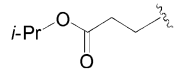
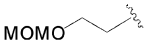
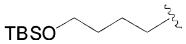
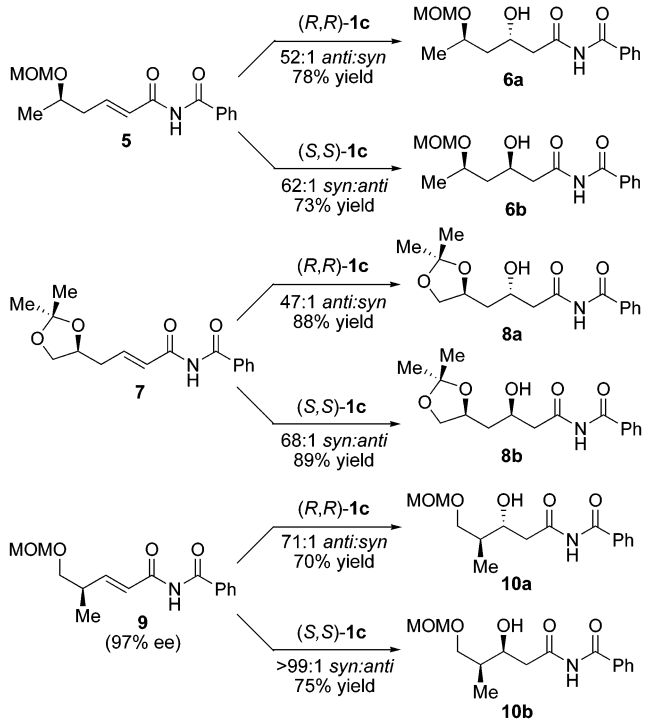
Table 1. Two-Step Enantioselective Synthesis of β-Hydroxy Imides



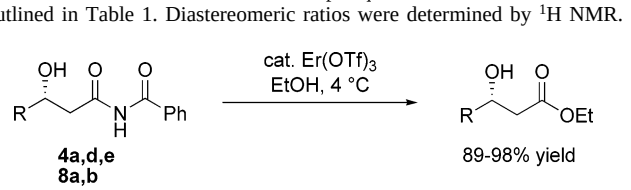
Product	R	conv. (%)/ee (%) (oxime ether)[a]	yield[b] (%)
4a	Me	>95/97	90
4b	Et	>95/98	93
4c	*i*-Pr	90/98	81
4d		>95/97	88
4e		95/97	88
4f		>95/97	82[c]

[a] Conversion determined by ^{1}H NMR, ee determined by chiral HPLC (Chiralpak AD column) of the intermediate oxime ether adduct. [b] Isolated yield over two steps, after chromatography, from reactions carried out on 0.5 mmol scale. [c] A yield of 80% was obtained for the two-step sequence carried out on 1.08 g (3.0 mmol) scale.

Scheme 2. Diastereoselective, Catalyst-Controlled, Two-Step Hydration of Chiral, Nonracemic α,β-Unsaturated Imides[a]



[a] Reaction conditions for the two-step sequence were identical to those outlined in Table 1. Diastereomeric ratios were determined by ^{1}H NMR.



derived from **4a** is ethyl (*S*)-3-hydroxybutyrate, a commercially available substance.[14]

We have developed the first catalytic asymmetric conjugate addition of an oxygen-centered nucleophile to unsaturated carboxylic acid derivatives. When combined with efficient *N*−*O* bond hydrogenolysis, this (salen)aluminum-catalyzed reaction enables the net enantioselective hydration of electron-deficient olefins with no need for purification of the intermediate oxime ethers.

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

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(6) The pK_a range for nucleophiles that have demonstrated utility in these conjugate additions is approximately 4−12.

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(9) Many typical organic solvents were tested, and alkane solvents proved vastly superior with respect to reaction rate. The results with cyclohexane and hexanes were comparable, while aromatic solvents led to much slower reactions. Chlorinated and ethereal solvents were poor media for the oxime addition reaction.

(10) Salicylaldoxime (*o*-hydroxybenzaldehyde oxime) is the least expensive commercially available benzaldoxime derivative (Aldrich 2003−2004 catalogue: U.S. $36.10/100 g). For the results of a broad screen of oximes for this reaction, see the Supporting Information.

(11) Substrates in which the β-substituent is aromatic, or aliphatic but much bulkier than *i*-Pr, suffer from competitive 1,2-addition of the oxime to both imide carbonyls. Highly insoluble substrates, such as those containing carbamate- or phthalimide-protected primary amines, also proved unreactive.

(12) To assess the intrinsic diastereofacial selectivities of these substrates, we performed the addition reactions using an achiral variant of the (salen)Al catalyst derived from ethylenediamine; however, this catalyst preferentially promoted the 1,2-addition of the oxime nucleophile to the imide carbonyls. Analysis of the crude reaction mixtures indicated that a small amount of the desired conjugate addition products were formed in roughly equimolar quantities with substrates **5**, **7**, and **9**. An important feature of these catalyst-controlled diastereoselective applications is the lack of intrinsic facial bias of the substrates. The preparation of analogous products by diastereoselective acetate aldol chemistry would likely be subject to relatively high intrinsic facial selectivities that might be difficult to override. Substrates **5**, **7**, and **9** were chosen to be representative of the most typically encountered motifs in polyketide chemistry, the area for which this method is most likely best suited.

(13) The isolated yields of products **6**, **8**, and **10** correlate directly with conversions in the oxime addition reactions (determined by ^{1}H NMR): **6a** (84%), **6b** (81%), **8a** (92%), **8b** (92%), **10a** (75%), **10b** (83%).

(14) See Supporting Information for details.

(15) Attempted ethanolysis of product **4f** was complicated by partial competitive desilylation. This product could be converted to the corresponding Weinreb amide in 88% yield. See Supporting Information for details. This useful transformation should be applicable to the other β-hydroxy imide products.

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