VIP Asymmetric Catalysis

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Achieving Molecular Complexity by Organocatalytic One-Pot Strategies—A Fast Entry for Synthesis of Sphingoids, Amino Sugars, and Polyhydroxylated α-Amino Acids**

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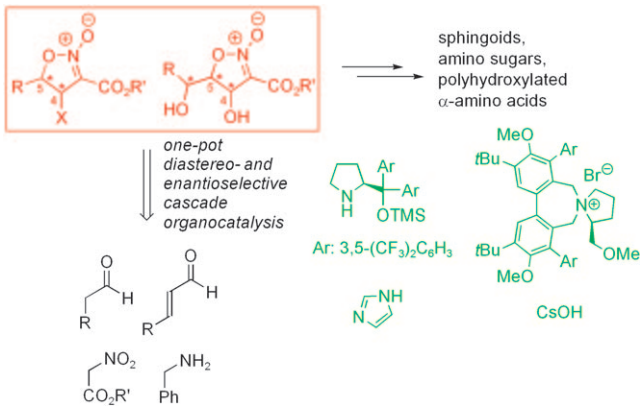
A major driving force for the intriguing developments in the field of total synthesis over the past century is the proficiency with which biological systems transform simple starting materials into complex molecular frameworks. Although necessary issues such as selectivity and synthetic efficiency to construct intricate biological structures can be addressed nowadays to a high degree, new aspects such as diversity and operational efficiency are becoming more important, because of the demand for making complex molecular architectures by effective and simple methodologies.[1] In this respect, catalytic cascade reactions involving two or more selective transformations in one pot are emerging as an attractive tool to overcome the operational limitations associated with traditional "Stop-and-Go" synthesis.[2]

Organocatalysis has been shown to be a powerful tool for forming multiple stereocenters in a one-pot protocol by employing either a single catalyst[3a–k] or a combination of catalysts.[3i–l] We became interested in the 4,5-disubstituted isoxazoline-*N*-oxide motif, since it has the potential to serve as an important building block for diversity orientated total synthesis. Several approaches to isoxazoline-*N*-oxides are present in the literature either in a racemic fashion,[4] starting from enantiomerically pure compounds,[5] or by employing stoichiometric amounts of a chiral reagent.[6] We envisioned that 4,5-disubstituted isoxazoline-*N*-oxides having up to three stereocenters could be obtained through a highly stereoselective one-pot procedure using simple and commercially available starting materials in combination with one or two organocatalysts (Scheme 1).

Herein, we report a new enantio- and diastereoselective one-pot protocol to access 4,5-disubstituted isoxazoline-*N*-oxides, as well as demonstrate the use of this protocol for the de novo synthesis of β,γ-dihydroxylated and β,γ,δ-trihydroxylated α-amino acid derivatives, phytosphingosines, and amino sugars.



Scheme 1. Synthesis of 4,5-disubstituted isoxazoline-*N*-oxides by using organocatalysis. TMS = trimethylsilyl.

Recently, our group reported an efficient and highly enantioselective procedure for the formation of optically active α-bromo aldehydes.[7a,b] Encouraged by the size and leaving group ability of the bromine, we evaluated the possibility of an in situ entrapment, thereby, generating a new class of chiral 1,2-dielectrophiles to participate in multiple-bond-forming cascade sequences. To our delight, the chirality stored within this α-carbonyl sp^3-carbon center, formed by the direct α-bromination of aldehydes **1** by the electrophilic bromination reagent **2** catalyzed by the TMS-protected diaryl-prolinol **3**, is fully exploited by a base-promoted face-selective Henry addition of nitroacetates and subsequent stereospecific O-alkylation, furnishing the enantio- and diastereoselective synthesis of 4,5-disubstituted isoxazoline-*N*-oxides **4** in one pot (Table 1). The generality of this one-pot, three-step sequence was explored and the results are outlined in Table 1. It appears that β-branched aldehydes **1a–c** provided the 4,5-disubstituted isoxazoline-*N*-oxides **4a–c** as single diastereomers in high yield (68–85%) and excellent enantioselectivity (94–96% *ee*; Table 1, entries 1–3). Nonconjugated unsaturated systems **1d** and linear unbranched substrates **1e–f** were also well-tolerated, giving the isoxazoline-*N*-oxide products **4d–f** in yields of 50–90%, d.r. values ranging from 73:27 to greater than 20:1, and *ee* values of 92–94% (Table 1, entries 4–8).

To expand the product diversity, the described three-step, one-pot protocol was extended to the formation of the corresponding Schiff base of the α-bromoaldehyde, which subsequent to an aza-Henry/alkylation cascade provided the

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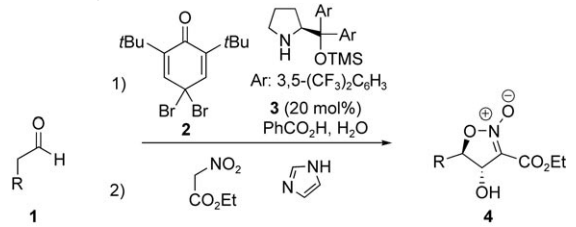
Table 1: Scope of the enantioselective α-bromination/Henry reaction/cyclization sequence.[a]



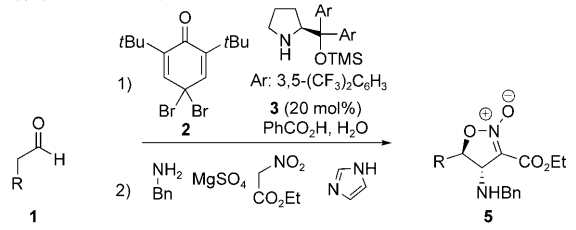
Entry[a]	**1** (R)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (*i*Pr)	**4a**: 77	>20:1	95
2	**1b** (*c*Pent)	**4b**: 86	>20:1	96
3	**1c** (*c*Hex)	**4c**: 68	>20:1	96
4	**1d** (*cis*-2-pentenyl)	**4d**: 85	>20:1	94
5[e]	**1e** (*n*Bu)	**4e**: 69	77:23	93 (93)
6	**1f** ($C_{15}H_{31}$)	**4f**: 90	73:27	94 (94)
7[e,f]	**1f** ($C_{15}H_{31}$)	**4g**: 50	79:21	94 (94)
8[e,g]	**1f** ($C_{15}H_{31}$)	*ent*-**4g**: 66	79:21	92 (92)

[a] Reactions performed on 0.2 mmol scale (see the Supporting Information). [b] Yield of the products isolated as a mixture of diastereoisomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC methods on a chiral stationary phase (see the Supporting Information). The value in parentheses is the *ee* value for the minor diastereoisomer. [e] *tert*-Butyl nitroacetate used as the nucleophile. [f] Reaction performed on a 2 mmol scale. [g] The enantiomer of catalyst **3** was used.

4-amino isoxazoline-*N*-oxides **5** in one operation (Table 2). As exemplified by the cascade reaction of aldehydes **1a**, **b**, and **d**, good yields and diastereoselectivities of **5a–c** were achieved during this four-step sequence. However, the Schiff base is prone to rapid enamine formation, leading to a slight decrease in the observed optical purity of the products (Table 2, entries 1–3).

Having been successful in our approach to the development of the one-pot cascade procedure for the formation of the optically active 4,5-disubstituted isoxazoline-*N*-oxides **4** and the 4-amino isoxazoline-*N*-oxides **5**, we decided to expand this organocatalytic chiral leaving group strategy to include the use of chiral epoxy aldehydes, generated by aminocatalysis, which would result in the creation of one additional stereocenter. This approach utilizes the organocatalytic epoxidation of α,β-unsaturated aldehydes **6** by hydrogen peroxide and TMS-protected diarylprolinol **3** as the catalyst.[7c] Preliminary results indicated that the epoxy motif gave poor or no selectivity in the subsequent Henry reaction, in which weak bases such as imidazole were applied. A thorough screening of diverse chiral and nonchiral bases and hydrogen-bonding catalysts favored the use of solid CsOH as the base under phase-transfer conditions, with the Lygo-type chiral ammonium salt **7** as the catalyst[7d] (Table 3). Aromatic, aliphatic, and functionalized α,β-unsaturated aldehydes **6a–c** all participated in the desired reaction sequence, assembling highly enantioenriched to enantiopure products in moderate to good yields and diastereoselectivities (Table 3, entries 1–3).

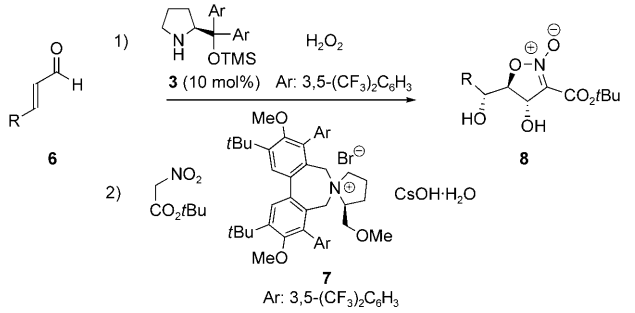
Table 2: Extension to an enantioselective α-bromination/imination/aza-Henry/cyclization sequence.[a]



Entry[a]	**1** (R)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (*i*Pr)	**5a**: 57	>20:1	86
2	**1c** (*c*Hex)	**5b**: 47	>20:1	81
3	**1d** (*cis*-2-pentenyl)	**5c**: 47	>20:1	82

[a] Reactions performed on a 0.2 mmol scale (see the Supporting Information). [b] Yield of the products isolated as a mixture of diastereoisomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC methods on a chiral stationary phase (see the Supporting Information).

Table 3: Enantioselective epoxidation/Henry reaction/cyclization sequence.[a]

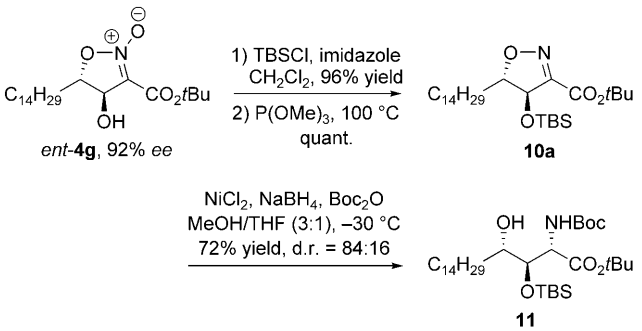


Entry[a]	**6** (R)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**6a** (*i*Pr)	**8a**: 71	73:27	99 (99)
2	**6b** (Ph)	**8b**: 65	78:22	99 (99)
3	**6c** (CH_2OBn)	**8c**:67	73:27	94 (94)

[a] Reactions performed on a 0.2 mmol scale (see the Supporting Information). [b] Yield of the products isolated as a mixture of diastereoisomers. [c] Determined by ^{1}H NMR spectroscopy. The relative and absolute configurations of the products were determined by NOE experiments or by analogy to known compounds. [d] Determined by HPLC methods on a chiral stationary phase (see the Supporting Information). The value in the parentheses is the *ee* value for the minor diastereoisomer.

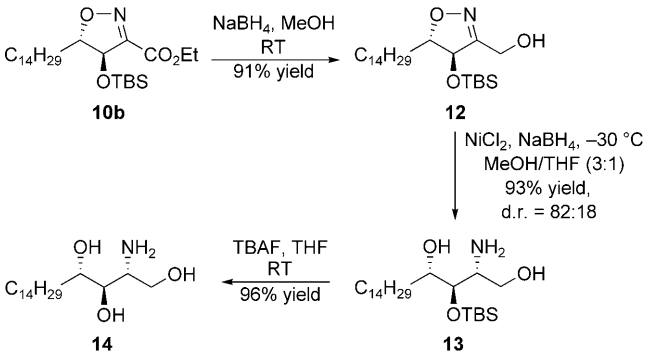
The diversity in the transformations of the obtained isoxazoline-*N*-oxide products **4, 5**, and **8** is demonstrated by their rapid conversion into important and biorelevant natural and non-natural products. Starting from *ent*-**4g**, the β,γ-dihydroxylated α-amino acid ester **11** can be formed in three high yielding steps, while maintaining the enantiomeric excess obtained in the one-pot cascade reaction, including O-protection with TBS (**9a**; see the Supporting Information), deoxygenation to **10a**, and reductive ring-opening (**11**) as presented in Scheme 2.

Sphingoid bases, such as sphingosine, phytosphingosine, and sphinganine, which are amide-linked with a fatty acid chain, form the indispensable structural motif of sphingolipids found in all eukaryotic cell membranes. Moreover, sphingolipids and their metabolites have been recognized to actively



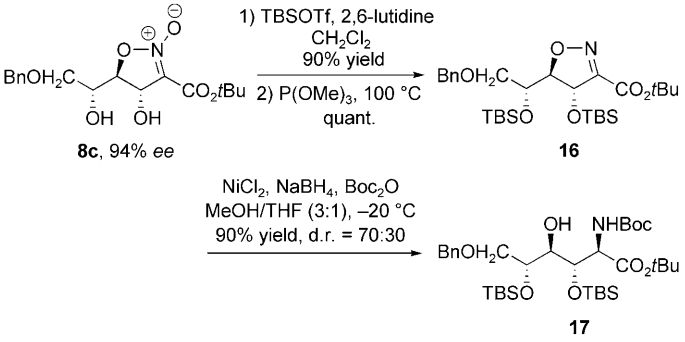
Scheme 2. Transformation of an isoxazoline-*N*-oxide into a β,γ-dihydroxylated α-amino acid derivative. TBS = *tert*-butyldimethylsillyl, Boc = *tert*-butoxycarbonyl.

participate in various signal transduction pathways as secondary messengers, thereby, playing an essential role in vital functions; for example, stress response regulation, cell cycle arrest, cell differentiation, and apoptosis.[8] Because of their biochemical significance and relevance, naturally occurring or chemically modified sphingoids and their analogues are considered attractive targets in total synthesis.[9] Initial predictions suggested that the reduction of the *tert*-butyl ester moiety of **10a** and subsequent global deprotection would provide the phytosphingosine product in a concise manner. However, several attempts failed; the use of the *t*Bu ester in the 4,5-disubstituted isoxazoline-*N*-oxide had to be avoided to suppress undesired side reactions. Only low yields were obtained using $LiAlH_4$ as the reductant, and subsequent O-silyl deprotection provided the known *N*-Boc L-*Ribo*-phytosphingosine.[9a] Instead, by employing the 4,5-disubstituted isoxazoline-*N*-oxide *ent*-**4f** as the initial chiral building block, the ethyl ester **10b** was successfully reduced, after deoxygenation and prior to ring-opening to provide the isoxazoline **12** (Scheme 3). Treatment of **12** with nickel borohydride and then removal of the silyl protecting group furnished L-*Ribo*-phytosphingosine (**14**) in 93% yield and 82:18 d.r. Interestingly, the hydroxymethyl group plays a crucial role in the sense of diastereoselectivity, since O-silylation (with a TBS group) resulted in only a 60:40 mixture of the diastereomers.



Scheme 3. Synthesis of L-*Ribo*-phytosphingosine (**14**). TBAF = *n*-tetrabutylammonium fluoride.

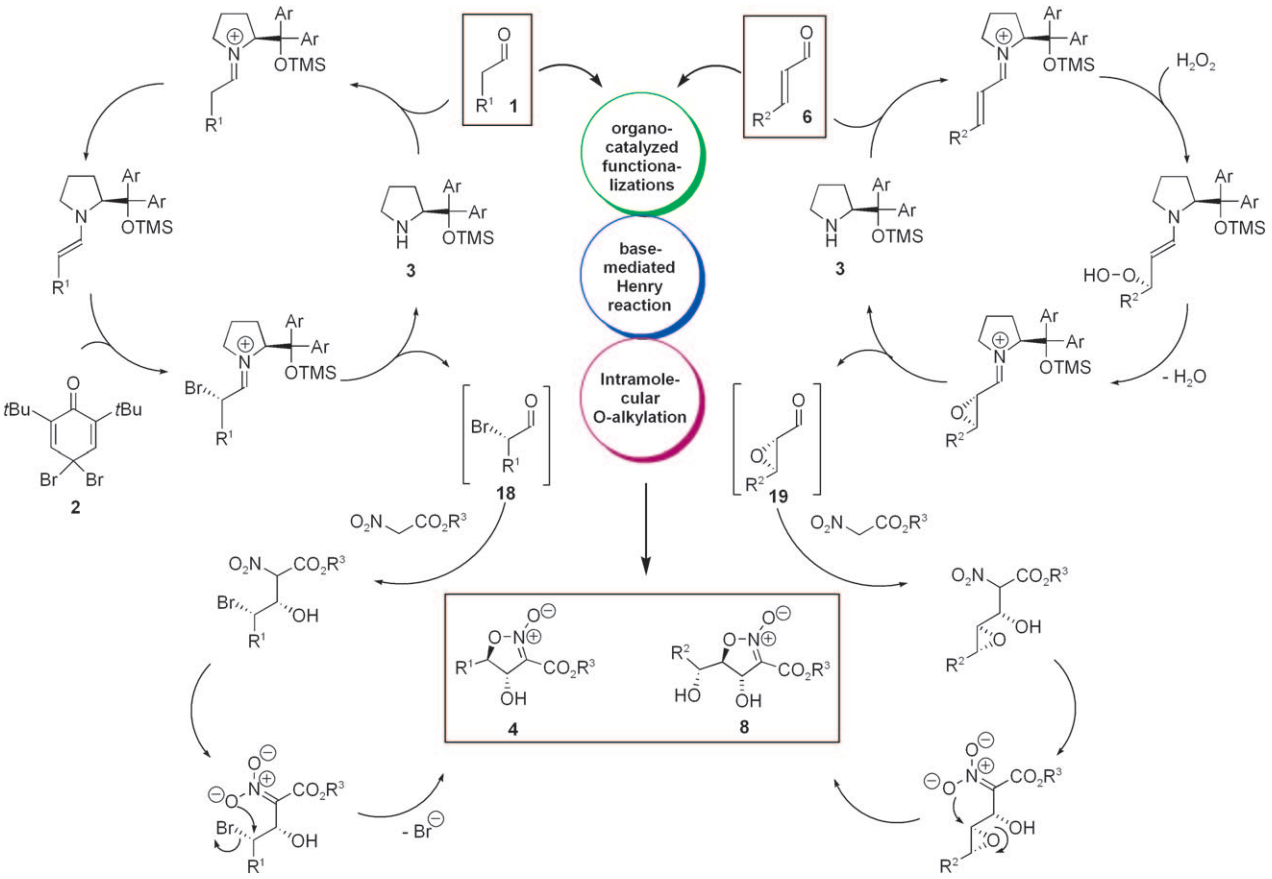
Product **8c**, obtained by the epoxidation/Henry alkylation cascade, contains three contiguous stereocenters and may serve as a fast entry into polyfunctionalized synthetic targets. The concept is demonstrated in Scheme 4. Starting from **8c**, the protection of the hydroxy groups with TBS (**15**; see the Supporting Information) and then deoxygenation leads to compound **16**, which is reductively cleaved to provide the β,γ,δ-trihydroxylated α-amino acid derivative **17**.



Scheme 4. Transformation of an isoxazoline-*N*-oxide into the β,γ,δ-trihydroxylated α-amino acid derivative **17**. Bn = benzyl, Tf = trifluorosulfonyl.

The product **17** is also a member of the 2-amino 2-deoxyaldonic acid class of compounds, which are highly relevant in carbohydrate chemistry as equivalents of amino sugars and other sugar derivatives—motifs frequently observed in antibiotics and macromolecules of living tissues.[10] Moreover, these 2-amino hexonates have also been adopted as intermediates in several total syntheses of natural products or fungicides.[11] Our approach to this class of compound has the advantage over traditional enantiomerically pure compound synthesis because of the potential for the simple introduction of orthogonal protecting groups, which makes easier the efforts for additional synthetic manipulations.

The mechanistic proposals for our one-pot reactions are outlined in Scheme 5. Saturated aldehydes **1** enter the catalytic cycle by condensation with the organocatalyst **3**, thereby forming a reactive enamine species, which reacts with the electrophilic bromination reagent **2** to introduce the α-bromine in an enantioselective manner. Upon hydrolysis and liberation of the catalyst **3**, the optically active α-bromo intermediate **18** is formed (Scheme 5, left). Alternatively, by employing α,β-unsaturated aldehydes **6** as substrates, an activated iminium ion is obtained as result of the condensation with **3** (Scheme 5, right). Next, the conjugate addition of hydrogen peroxide, subsequent epoxide formation, and then catalyst hydrolysis provides the enantiomerically enriched *trans*-epoxyaldehydes **19**. Having completed the initial organocatalyzed functionalization cycles, aldehydes **18** and **19** are subjected to a base-induced intermolecular Henry reaction with nitro acetates as nucleophiles. Subsequent deprotonation of the carbon atom α to the nitro group, and intramolecular S_N2-type O-alkylation utilizing either the bromine or epoxide as chiral leaving groups, furnished the highly functionalized



Scheme 5. Mechanistic proposal for the one-pot reactions.

isoxazoline *N*-oxide products **4** and **8**, respectively, in one-pot (Scheme 5, bottom).

In conclusion, we have demonstrated that by utilizing an organo-mediated chiral leaving group strategy, molecular complexity can be rapidly and efficiently achieved from simple and commercially available starting materials, with minimal manual operations. The 4,5-disubstituted isoxazoline-*N*-oxide products, obtained in high yields and excellent enantioselectivities, serve as versatile building blocks for natural product synthesis, as exemplified by the *de novo* synthesis of *Ribo*-phytosphingosine, amino sugar derivatives, and polyfunctionalized α-amino acid derivates.

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