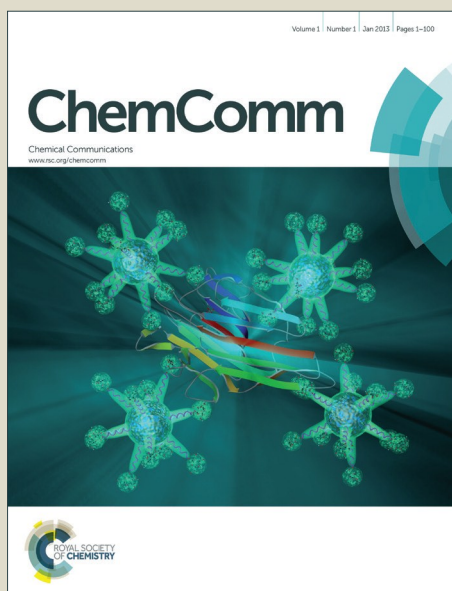


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ARTICLE

Stereoselective organocatalytic oxidation of alcohols to enals: A homologation method to prepare polyenes†

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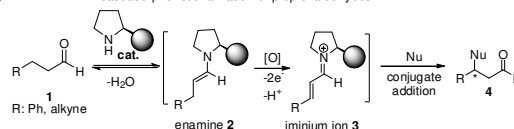
Xiaobei Chen,^{†ac} Yinan Zhang,^{†b} Huixin Wan,^d Wei Wang,^{*bc} Shilei Zhang^{*a}

A novel organocatalytic oxidation through oxidative enamine catalysis was developed with excellent compatibility for the direct syntheses of enals from simple saturated alcohols. By using this amine-catalyzed IBX-oxidation, a wide range of aromatic and aliphatic substituted enals were successfully generated in high yields and exclusively stereoselective E-geometry. Moreover, varying the solvents and/or the loading amounts of IBX allowed for the selective oxidation of alcohols and aldehydes. Importantly, the homologous application of this method provided a selective and efficient way of preparing various highly sensitive conjugated polyene frameworks, which are enriched in natural products.

The establishment of organocatalysis as one of the three major catalytic reaction modes in the last 15 years is a cornerstone in organic synthesis.¹ The most notable characteristics of this catalytic mode maybe attributed to the ability of aminocatalysts to promote reactions by energetically raising HOMO,² lowering LUMO,³ and activating singly occupied molecular orbital (SOMO).⁴ Although these three activation modes involve most enamine and iminium organocatalysis, the search for new aminocatalytic methods and their application to access highly functionalized building blocks remains a challenge. Recently, we and Hayashi independently discovered an interesting enamine catalytic mode with a key dehydrogenation step involving a 2e⁻-transfer process mediated by o-iodoxybenzoic acid (IBX).⁵ As a result of the newly formed C=C bond of iminium ion **3** from the C-C bond of enamine **2**, this novel organocatalytic oxidative method could be used to prepare β-functionalized aldehyde **4** in a cascade manner (Figure 1a). In the following work, we found that an alkyne-substituted iminium ion underwent hydrolysis in the absence of a nucleophile to deliver the corresponding α,β-unsaturated aldehydes; therefore, a practical method was devised for the total synthesis of the natural product dihydroxerulin.⁶ Because the sensitive alkyne intermediate of dihydroxerulin is compatible in this oxidative

enamine catalysis reaction, we conceived that this smooth method could be extended to form unsaturated aldehydes equipped with diverse functionalities. Likewise, together with

a) Previous work: cascade β-functionalization of propionaldehydes



b) This work: organocatalytic oxidation of propionalcohol and homologation to polyene

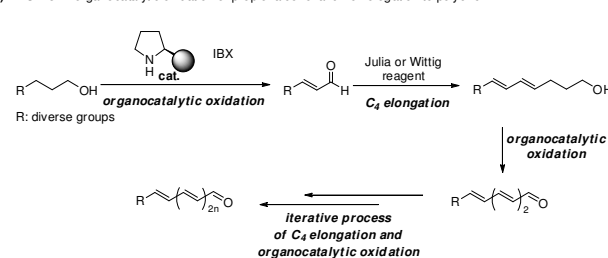


Figure 1. Oxidative enamine catalysis and its potential application in polyene homologation.

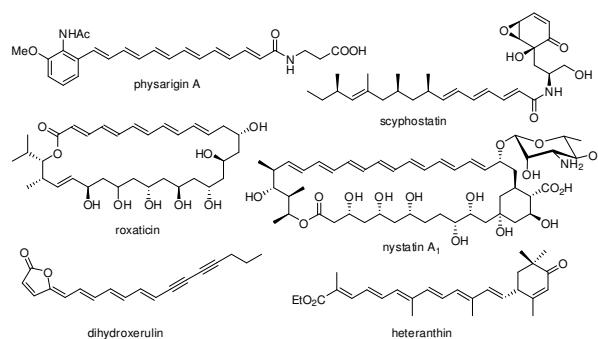


Figure 2. Selected examples of naturally occurring polyenes.

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C₄ elongation using olefination reagents, such as Julia reagent or Wittig reagent, general homologation of the amine-catalyzed oxidative process could be introduced to the saturated alcohols repeatedly. This allowed access to highly conjugated polyene architectures, which have served as important precursors for the total synthesis of natural products containing polyunsaturated hydrocarbons (Figure 1b).

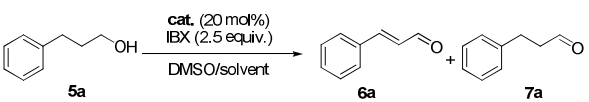
Polyenes are naturally abundant and structurally diverse natural products that have a variety of uses (Figure 2), such as antibiotics,⁷ pigments,⁸ and fluorescent probes.⁹ The contiguous conjugated olefin moieties in polyene architectures provide ideal prototypes to practice the homologation strategy, in which amine-catalyzed IBX-oxidation and C₄ elongation would be systematically repeated to assemble the contiguous conjugated structures. The most recent example¹⁰ was an elegant method that took advantage of stackable N-methyliminodiacetic acid (MIDA) boronates¹¹ to synthesize various naturally occurring polyene scaffolds with high stereocenter fidelities. However, due to the sensitivity of the contiguous double bond frameworks towards light, oxygen, temperature and acidic reagents, developing mild conditions with good geometric selectivity is highly demanded in polyene synthesis. As a mutual complement to transition-metal catalysis,¹² we herein describe the selective organocatalytic oxidation of alcohols to enals and its homologous application for the preparation of various polyene architectures that are enriched in natural products.

The model reaction of 3-phenylpropan-1-ol was initially examined at room temperature with optimal solvent conditions (Table 1).⁶ It was found that catalyst **IV** was the best catalyst in proceeding organocatalytic oxidation and yielded the desired cinnamaldehyde in 82% yield (entries 1–4). This observation could be attributed to appropriate hydrogen bonding interactions between the hydroxyl groups of catalyst **IV** and IBX, which could have benefited the interaction of IBX with the substrates and accelerated the reactions. The yield was further increased to 85% when a stepwise one-pot procedure was used (entry 5). Both procedures exclusively generated *E* geometric cinnamaldehyde, and no saturated aldehyde intermediate **7a** was observed in the NMR of the crude reaction mixture. In comparison, the reaction stopped at the alcohol oxidation stage to produce 3-phenylpropanal (**7a**) in the absence of a secondary amine catalyst, which verified the critical role of the organocatalytic transformation from enamine to the corresponding iminium in the formation of olefinic bonds (entry 6).

Under the optimal reaction conditions, an investigation of the reaction scope and generality was conducted, and the results are summarized in Figure 3. Substrates incorporating various substituted phenyl rings were well tolerated, furnishing the corresponding enals **6a–h** in excellent yields and *E/Z* selectivity. Different electronic properties and substituent positions had little impact on the reactivities. Substrates with hetero-aromatic rings were also competent and gave yields ranging from 78% to 86% (**6i–k**). Remarkably,

organocatalytic g-oxidation was observed with substrate **5l**. We speculate that the production of dienal **6l** was the result of duplex enamine oxidation. The second enamine oxidation happened at the g-position of the enal intermediate, which was initially formed by the first enamine oxidation reaction. The relatively low yield was ascribed to polymerization of the starting materials and of the intermediates under the given conditions.¹³ As the first reported duplex enamine oxidation, this cascade conversion provides direct access to dienals from simple alcohols.

Table 1. Optimization of reaction conditions for organocatalytic oxidation of 3-phenylpropan-1-ol (**5a**) to cinnamaldehyde (**6a**).^a



Reaction scheme showing 3-phenylpropan-1-ol (**5a**) reacting with catalyst (20 mol%), IBX (2.5 equiv.), and DMSO/solvent to produce cinnamaldehyde (**6a**) and 3-phenylpropanal (**7a**).

Catalysts shown: **I** (N-methyliminodiacetic acid boronate), **II** (N-methyliminodiacetic acid boronate), **III** (N-methyliminodiacetic acid boronate), **IV** (N-methyliminodiacetic acid boronate).

entry	solvent (v/v = 1/1.5)	catalysts	% Yield ^a 6a/7a	<i>E/Z</i> ^b 6a
1	DMSO/CH ₃ CN	I	72/0	10/1
2	DMSO/CH ₃ CN	II	65/5	8/1
3	DMSO/CH ₃ CN	III	0	-
4 ^c	DMSO/CH ₃ CN	IV	82/0	>20/1
5 ^d	DMSO/CH ₃ CN	IV	85/0	>20/1
6 ^c	DMSO/CH ₃ CN	-	0/90	-

^a Reaction conditions: unless specified, alcohol **5a** (0.15 mmol), IBX (0.375 mmol, 2.5 equiv.) and the catalyst (0.03 mmol) were dissolved in 0.5 mL of solvent and stirred at rt for 8 h. ^b The product ratios and double bond geometric ratios were determined by ¹H NMR analysis of the crude product using *p*-nitrobenzaldehyde as internal standard. ^c Isolated yields. ^d Alcohol (0.15 mmol) and IBX (0.225 mmol, 1.5 equiv.) in DMSO were first mixed and stirred for 2 h at rt; then, IBX (0.15 mmol), catalyst **IV** (0.03 mmol), and CH₃CN were added to the mixture and stirred for 8 h at rt.

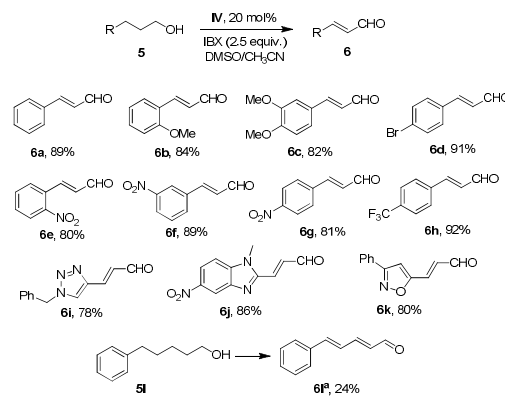
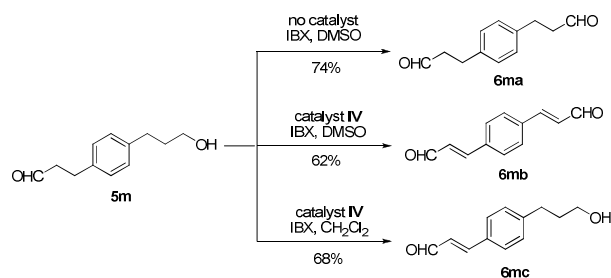


Figure 3. Substrate scope of the organocatalytic oxidation of aromatic propanols to enals. Reaction conditions: a solution of alcohol **5** (0.15 mmol) in DMSO (0.3 mL) and CH₃CN (0.45 mL) was treated with IBX (2.5 eq) and catalyst **IV** (20 mol %) for 4–24 h at rt. All the crude products were first checked with ¹H NMR to show exclusive *E* selectivity (>20/1). ^a 4 eq of IBX was used.



Scheme 1. Selective oxidation of substrate **5m**.

To understand the differences in oxidative reactivity between aldehydes and alcohols, we designed bifunctional substrate **5m** that had a para-substitution of propanol and propional (Scheme 1). Universal IBX oxidation in DMSO without organocatalyst **IV** predominantly gave symmetric aldehyde **6ma** in 74% yield without any formation of olefinic bonds. Meanwhile, treatment with a catalytic amount of **IV** facilitated enamine oxidation to form symmetric α,β -unsaturated aldehyde **6mb** in 62% yield. Notably, selective dehydration occurred only on the aldehyde branch of the substrate to produce **6mc** when dichloromethane was used as a solvent. The alcohol branch was not involved in the reaction probably because the non-polar solvent environment inhibited the common alcohol oxidation reaction,^{5a} which is different from Nicolaou's ketone/aldehyde dehydration protocol.¹⁴

After exploring the scope of aromatic propanols, we were intrigued about the substrate compatibility of other γ -functionalities, especially those containing C=C bonds, for the possibility of discovering a homologous model. As shown in Figure 4, we found that organocatalytic oxidation underwent smoothly with a variety of γ -SP² carbons, furnishing the desired diene/trienealdehydes **8a-h** in good yields and exclusive *E*-selectivities. The tolerant functionalities included

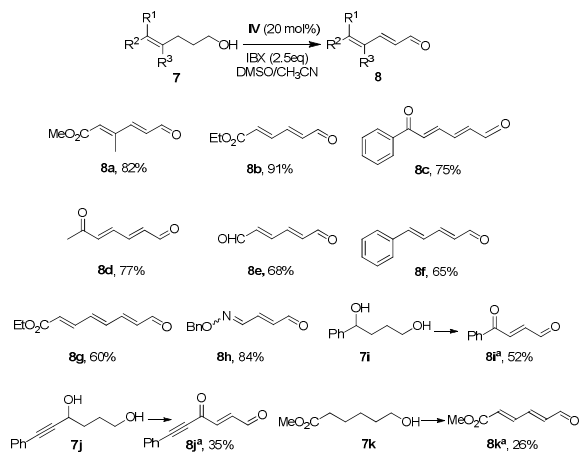


Figure 4. Substrate scope of the organocatalytic oxidation of propanols with a γ -SP² carbon. Reaction conditions: a solution of alcohol **7** (0.15 mmol) in DMSO (0.3 mL) and CH₃CN (0.45 mL) was treated with IBX (2.5 eq) and catalyst **IV** (20 mol %) for 2–24 h at rt. All the crude products were first checked with ¹HNMR to show exclusive *E* selectivity (>20/1). ^a 5 eq of IBX was used.

α,β -unsaturated esters (**8a-b**), ketones (**8c-d**), an aldehyde (**8e**), a styrene (**8f**), a diene ester (**8g**), and a Schiff base (**8h**). It is worth noting that secondary alcohols **7i** and **7j** were also converted to the desired 4-oxo-2-enals in moderate yields with an increasing amount of IBX. Likewise, duplex enamine oxidation also took place on alcohol **7k** to produce **8k**, which could serve as a useful building block to generate a number of polyene natural products.¹⁵

To demonstrate the robustness of the amine-catalyzed IBX-oxidation reactions, we selected some representative and interesting substrates, such as **5a**, **5d**, **5k**, **7b**, **7h**, and **7i**, for scale-up experiments (3 mmol). The yields (see Supporting Information) were similar to those of the small-scale results listed in Figure 3 and Figure 4.

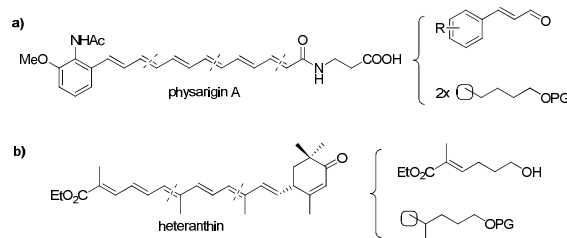
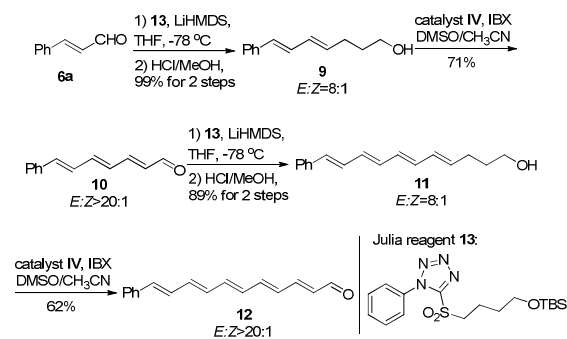
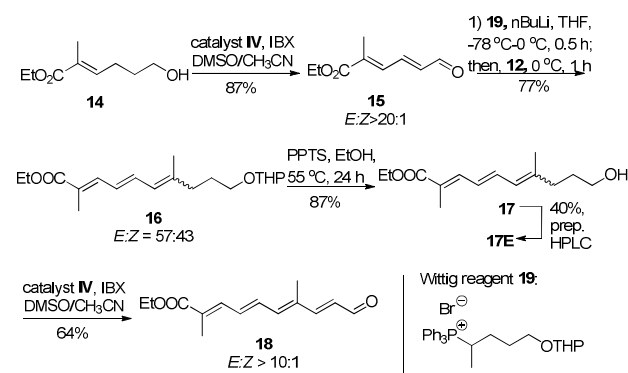


Figure 5. Retrosynthetic analysis of polyene frameworks using homologous strategy of the organocatalytic oxidation.



Scheme 2. The homologous process to the polyene architecture by sequential Julia-Kocienski olefination and organocatalytic enamine oxidation.



Scheme 3. The homologous process to the polyene architecture by sequential Wittig olefination and organocatalytic enamine oxidation.

Encouraged by the excellent compatibility of the organocatalytic oxidation reaction, we further targeted a homologous strategy to construct polyene architectures. According to the strategy described in Figure 1b, the polyene framework can be dissected into several butanol C₄ templates (Figure 5). For example, a physarigin A framework that contains six contiguous *E* double bonds can be divided into cinnamaldehyde and two copies of butanol fragments. Meanwhile, heteranthin that bears six contiguous methyl substituted olefinic bonds can be split into a hexenoate and an isopentanol fragment. The amine-catalyzed IBX-oxidation can be applied directly to alcohols for the formation of α,β -unsaturated aldehydes, and C₄ fragments can be conveniently assembled to the terminal aldehyde group by using Julia or Wittig reagent for chain elongation. Thus, the iterative process of organocatalytic oxidation and C₄ elongation could provide a simple, efficient and modular way for synthesizing polyene architectures.

After the preparation of Julia reagent **13**, elongation of cinnamaldehyde **6a** under cryogenic conditions followed by TBS deprotection offered propanol alcohol precursor **9** with good *E* stereoselectivity (Scheme 2). Precursor **9** was then subjected to an organocatalytic oxidative reaction to generate triene aldehyde **10** in 71% yield with exclusive *E* configuration. The iterative process of elongation and oxidation was performed to homologously assemble another C₄ fragment to prepare physarigin A framework **12** by repeating the sequential Julia-Kocienski¹⁸ and amine-catalyzed IBX-oxidation reactions. For the methyl substituted polyene framework, hexenoate **14** was first oxidized to dial **15** using organocatalytic oxidation (Scheme 3). Elongation of the aldehyde with Wittig reagent¹⁹ afforded triene **16** with an *E/Z* ratio of 57:43. The *E* stereomer **17E** was isolated by preparative HPLC after tetrahydropyran deprotection. Iterative amine-catalyzed IBX-oxidation eventually provided homologous tetraene **18**, a heteranthin framework with exclusive *E* configuration, which was confirmed by 2D NMR spectra. Finally, considering the potent and practical role of the aldehyde precursors generated by organocatalytic oxidation, application of this homologous strategy with diverse butanol building blocks could result in a large range of natural polyenes and natural polyene-like derivatives that could be used for the total synthesis of natural products and screening of bioactive compounds²⁰ as drug candidates in medicinal chemistry.

In conclusion, we have developed an amine-catalyzed IBX-oxidation strategy through the unprecedented oxidative conversion of enamine to iminium. This smooth synthetic method features: 1) the selective and efficient conversion of simple saturated propanols and propionaldehydes to polyunsaturated aldehydes; 2) a high tolerance for substrates, including various γ -SP² functionalities; and 3) an unprecedented oxidative process with high yields and exclusive geometric *E* selectivities. Furthermore, we also developed a homologous strategy using an iterative process of elongation and oxidation that enables the syntheses of various natural polyene frameworks, thus setting the stage for potential access to natural polyenes and their derivatives.

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