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Tandem aminoxylation–allylation reactions: a rapid, asymmetric conversion of aldehydes to mono-substituted 1,2-diols†

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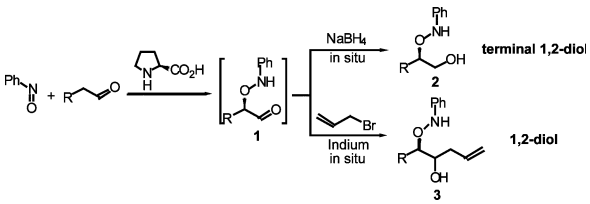
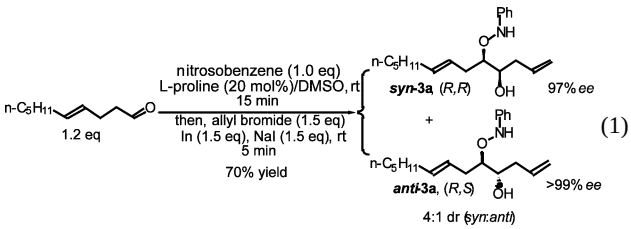
A facile and rapid synthesis of enantiopure mono-substituted 1,2-diols was achieved by the tandem aminoxylation–allylation reactions of aldehydes.

1,2-Diols[1] play an important role in biological systems. They have also found frequent use as starting materials for the enantiospecific synthesis of natural products and drugs,[2] as chiral auxiliaries and as transition metal ligands for asymmetric synthesis and catalysis.[3] Several methods for the synthesis of these units have been developed. Among them, Sharpless asymmetric dihydroxylation (AD) of (*E*)-olefins is the most efficient and practical process, giving rise to *syn*-1,2-diol products in high enantiomeric excesses (*ee*'s).[1a,4] However, Sharpless AD of (*Z*)-olefins leading to *anti*-1,2-diols shows low enantioselectivity.[4b] The direct catalytic asymmetric aldol reactions using α-hydroxyketones as donors provide an alternative to the AD, realizing a high degree of enantioselectivities to afford 1,2-diols directly.[5] These approaches involve the simultaneous generation of a C–C bond with two adjacent stereocenters, but allow only limited types of substituents. For example, either aliphatic[5a] or aromatic[5b,c] α-hydroxyketones must be employed in the aldol reactions. Moreover, the longer reaction time is required to accomplish the reaction (*e.g.* 24–72 hours needed in the direct aldol reactions[5]). Recently, we discovered the direct catalytic asymmetric α-aminoxylation of aldehydes by using enantiopure proline as catalyst and nitrosobenzene as the oxygen source.[6] Although the α-aminoxy aldehyde intermediates **1** formed in the reaction could not be isolated in good yields, they could be trapped by the *in situ* reduction to convert to the terminal 1,2-diol units **2** in good yields with excellent enantioselectivities. Based on this, we describe herein a continuation of the study, a highly enantioselective one-pot route to non-terminal 1,2-diol units involving the proline catalyzed α-aminoxylation of aldehydes and followed by *in situ* indium-promoted allylation. This strategy allows a rapid enantioselective synthesis of both *syn*- and *anti*-mono amino-substituted 1,2-diols **3** in good yields (65–82%) with excellent enantioselectivities (*ee*'s from 97% to > 99%).



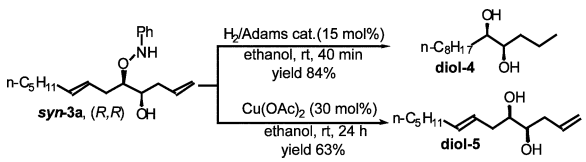
The effectiveness of the proline-catalyzed asymmetric α-aminoxylation of aldehydes[7] permits use of nearly stoichiometric amounts of both partners to complete the reaction in only 10 to 20 minutes with excellent *ee*'s. We became interested in whether the chiral α-*N*-phenylaminoxy aldehyde intermediates **1** generated in the α-aminoxylation could be trapped by the indium-promoted allylation *in situ* to form the non-terminal 1,2-diol units **3**. While the investigation of the stereochemical course of the indium-promoted allylations of α-hydroxyaldehydes revealed that excellent diastereoselectivity[8] operates, we started to test if an *in situ* allylation could stereoselectively convert the chiral intermediates **1** to the corresponding 1,2-diol units **3**.

Initial experiments were conducted by stirring *trans*-4-decenal (1.2 equiv.), nitrosobenzene (1.0 equiv.) and L-proline (20 mol%) in DMSO at room temperature. When the color of the reaction mixture turned to orange from green (in 15 minutes, the color change indicating the endpoint of the α-aminoxylation), allyl bromide (1.5 equiv.) and indium (1.5 equiv.) were added. Disappointingly, a complicated reaction mixture was found. We then tried to use water[9] as a co-solvent (DMSO/H_2O – 1 : 1) in the allylation step. This time the corresponding *syn*-/*anti*-**3a** was isolated as the major product after the allylation was performed for 10 minutes. However, the yield of the product **3a** was only 46% based on nitrosobenzene. Separation of *syn*-**3a** and *anti*-**3a** on a silica gel column further showed that no diastereoselectivity occurred in the allylation (*syn*-/*anti*-**3a** = 1 : 1), different from that observed with α-hydroxyaldehydes.[8] But, excellent enantioselectivities were found (both *syn*-**3a** and *anti*-**3a** with over 95% *ee*'s). Encouraged by these results, we turned our attention to using a promoter, with which the allylation could be accelerated. Since sodium iodide is known to increase the rate of the indium-mediated allylation of ketones with allyl bromide, we next investigated the *in situ* allylation with sodium iodide. Significantly, the allylation in the solvent DMSO was completed in just 5 minutes when 1.5 equiv. of sodium iodide was employed. The product *syn*-**3a** and *anti*-**3a** were isolated in good yield (70%, eqn. (1)) with the diastereoselectivity 4 : 1 (*syn*/*anti*). Determination of the enantioselectivities of *syn*-**3a** and *anti*-**3a** by chiral phase HPLC showed that excellent *ee*'s (*syn*-**3a** with 97% *ee* and *anti*-**3a** with over 99% *ee*) were obtained in the one-pot aminoxylation–allylation reaction.



(1)

Removal of the *N*-phenylamino group from product *syn*-**3a** was achieved either by catalytic hydrogenation[6] or by the copper(II) catalyzed N–O bond cleavage reaction.[10] For example, the catalytic hydrogenation of the *syn*-**3a** over platinum dioxide (Adams catalyst) cleaved the N–O bond, but at the same time it also reduced the two C=C bonds in the molecule affording the diol **4** as product in 84% yield. The copper(II) catalyzed N–O bond cleavage was different, giving the C=C bond untouched diol **5** as product in 63% yield (eqn. (2)). It should be pointed out that both N–O bond cleavage reactions did not result in any loss in enantiomeric purity.



(2)

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b314356b/

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To further explore the scope of the one-pot reactions, a series of aliphatic aldehydes were tried under the same reaction conditions. The experimental procedure involves only mixing and stirring, and comprises these steps: 1) the mixture of the aldehyde (1.2 equiv.), nitrosobenzene (1.0 equiv.) and the catalyst proline (20 mol%) in DMSO was stirred at ambient temperature for 10–20 minutes; 2) allyl bromide (1.5 equiv.), indium (1.5% equiv.) and sodium iodide (1.5 equiv.) were added and then the reaction mixture was kept stirring for 3–5 minutes. The reaction does not require anhydrous or oxygen-free conditions. Table 1 shows this chemistry. In every case, the tandem reactions afforded the products *syn*-/*anti*-**3b–3f** in good overall yields (65–82%) with excellent enantioselectivities (*syn*-**3b** to *syn*-**3f** with 98–99% *ee*'s and *anti*-**3b** to *anti*-**3f** with 97 – over 99% *ee*'s). The diastereomeric ratios (*dr*) ranged from 3 : 2 to 4 : 1. It is noteworthy that the terminal allylic group in the products **3a–3f** could be easily converted to new aldehydes for further dihydroxylation using the same tandem strategy, so that chiral polyols might be synthesized step by step. All racemic standard products required to establish HPLC conditions were made by using racemic proline.

The observed diastereoselectivity (*syn*-selective)[11] of the transformation is in accord with the previously proposed model for the indium promoted allylation.[8] When the hydroxyl group in the transition state is substituted by the *N*-phenylamino group, a big dropoff in π-facial discrimination materializes, presumably due to increased steric hindrance. This caused a decrease in diastereoselectivity while the unsubstituted α-hydroxyaldehydes gave excellent *dr*.[8b]

In conclusion, we have developed a highly efficient tandem aminoxylation–allylation reaction – the proline catalyzed asymmetric α-aminoxylation of aldehydes and subsequent *in situ* allylation – for the direct, rapid and enantioselective conversion of aldehydes to both *syn*- and *anti*-mono amino-substituted 1,2-diols in high yields with excellent enantioselectivities. Since proline is commercially available in both enantiomerically pure forms, this methodology provides an extremely facile route to all four stereoisomers of both *syn*- and *anti*-1,2-diols, important building blocks and ligands in organic synthesis and asymmetric catalysis. Studies on the further improvement of the diastereoselectivities of the allylation in the tandem reactions, on mechanistic and synthetic aspects as well as on combinatorial applications of this chemistry are currently ongoing.

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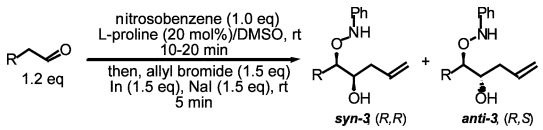
Table 1 One-pot asymmetric synthesis of both *syn*- and *anti*-diol units



Product	R	Yield[a]	*dr*[b] (*syn* : *anti*)	*ee*[c] (*syn*/*anti*, %)
3a		70%	4 : 1	97/> 99
3b	methyl	80%	3 : 2	98/98
3c	isopropyl	71%	5 : 3	99/97
3d	propyl	65%	3 : 2	98/98
3e	butyl	82%	3 : 2	98/98
3f	benzyl	74%	3 : 2	99/> 99

[a] All were yields of isolated products. [b] The *syn* : *anti* ratio was determined by weighing the separated isomers and/or by ^{1}H-NMR spectra. [c] The *ee*'s were determined by chiral phase HPLC columns (see Supporting Information).

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11 The stereochemistry of this tandem transformation was established by ^{1}H-NMR determination of *syn*- and *anti*-structures of the products together with the known absolute configuration of the α-aminoxyl aldehydes (see ref. 6).