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Dynamic kinetic resolution of 2-methyl-2-nitrocyclohexanol: Combining the intramolecular nitroaldol (Henry) reaction & lipase-catalysed resolution

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ABSTRACT

Efforts to combine the intramolecular nitroaldol reaction with lipase-catalysed resolution of the resulting nitroaldol adduct in a one-pot dynamic kinetic resolution (DKR) are described. Significant challenges were encountered in the combination of the two systems. *trans*-2-Methyl-2-nitrocyclohexyl acetate (±)-**3b** was isolated in excellent enantiopurity (>98% *ee*) *via* a sequential DKR sequence where the lipase-mediated resolution and base-mediated interconversion of 2-methyl-2-nitrocyclohexanol **2** were effected alternately, demonstrating the feasibility of this approach initially. Further work showed, for the first time, evidence that a DKR-type system is possible for **2**. Reaction engineering allowed the design of a sequential one-pot reaction system which furnished the products with excellent enantioselectivity, and good diastereoselectivity.

1. Introduction

The Henry reaction is an important base-mediated transformation in organic chemistry leading to vicinal nitroalcohols (Scheme 1), which can be converted into a wide variety of synthetic intermediates, such as 1,2-aminoalcohols and α-hydroxycarboxylic acids.[1–3] Although the reaction is known for decades, stereo- and diastereoselective approaches leading to enantiomerically pure nitroalcohols are still challenging. Principal approaches to the catalytic asymmetric nitroaldol reaction, including transition metal- and organo-catalysed methods, have been reviewed in detail.[2,4,5] In the past decade, there has been an emergence of biocatalytic protocols to resolve the products of the Henry reaction due to their mild reaction conditions and high selectivity.[6] There are two distinct biocatalytic methods; direct enzyme-catalysed (hydroxynitrile lyases) asymmetric nitroaldol reaction[7] or initial chemical formation of the β-nitroalcohol product followed by enzymatic kinetic resolution of the resulting stereoisomers. The latter suffers from the limitation of attaining a maximum theoretical yield of 50%. In recent years, we have developed an effective protocol for kinetic resolution of 2-nitrocyclohexanol **5**.[8] In this study, we attempted to develop a dynamic kinetic resolution for compound **5**, and expanded it to 2-methyl-2-nitrocyclohexanol **2**.

Previously, Vongvilai et al. have developed a procedure for the intermolecular dynamic kinetic resolution of β-nitroalcohols, but this was limited by the need to use a large excess of the nitroalkane in order to shift the equilibrium towards the formation of the product.[9,10] In our current study, we have the added challenge of a second stereocentre, leading to potential complexity in stereocontrol.

Herein, we report our studies, combining the reversible intramolecular base-catalysed nitroaldol reaction of 6-nitroheptanal **1** with a one-pot lipase-mediated acetylation and kinetic resolution of the subsequent β-nitroalcohol **2** leading to 2-methyl-2-

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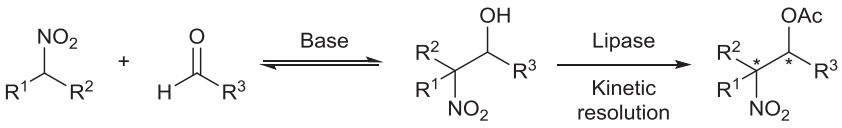


Scheme 1. DKR of the nitroaldol through lipase catalysis.

nitrocyclohexyl acetate **3** with moderate diasteroselectivity but excellent enantiopurity (Scheme 2). Ideally, this DKR would provide exclusive access to a single stereoisomer of **3**. To date limited research has been carried out in this area, and while the viability of a one-pot reaction combining the Henry reaction with enzyme-mediated dynamic resolution has previously been described, it is evident that there are significant limitations to be overcome before this protocol has a broad synthetic utility.[9–11]

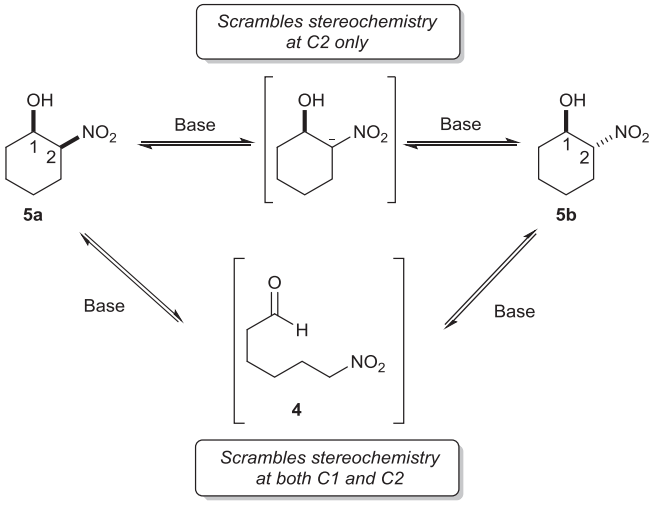
2. Results and discussion

2.1. Diastereoselective lipase-mediated transesterification

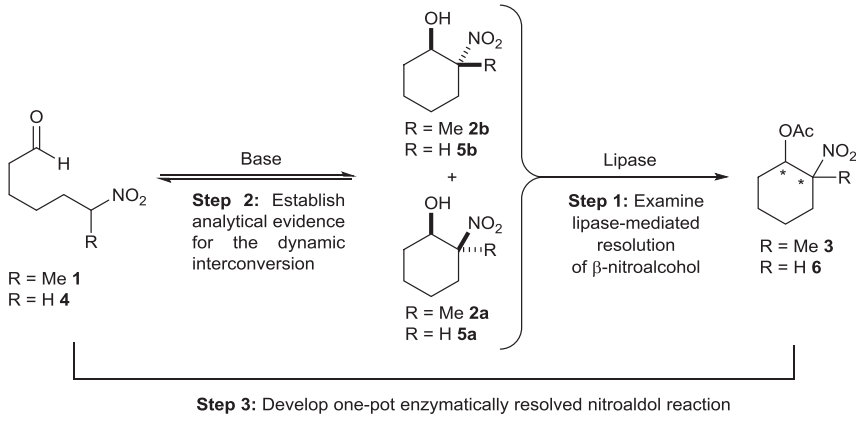
We have previously reported efficient kinetic bioresolution for both the *cis*- and *trans*-2-nitrocyclohexanols (±)-**5a** and (±)-**5b** *via* enzyme-mediated transesterification and ester hydrolysis.[8] While base-mediated interconversion of *cis*- and *trans*-2-nitrocyclohexanol (±)-**5a** and (±)-**5b** is readily established, initially believed to indicate reversible nitroaldol reaction, detailed investigation demonstrated that the interconversion was complicated due to competing epimerisation *via* deprotonation geminal to the nitro group (Scheme 3). Critically, when enantiopure *cis*- and *trans*-2-methyl-2-nitrocyclohexanol **5a** and **5b** are individually exposed to base, interconversion of **5a** and **5b** is seen but without stereochemical scrambling at C(1)OH centre. This can only be rationalised by deprotonation at the C(2)NO_2 centre, rather than a retro-Henry reaction. The interconversion of (±)-**5a** and (±)-**5b** *via* the reversible nitroaldol reaction is essential for a DKR approach as the alternative deprotonation pathway does not enable racemisation at the cyclohexanol stereogenic centre but only affects the centre bearing the nitro substituent. The complication of the competing pathway prevented the development of a one-pot intramolecular nitroaldol reaction of 6-nitrohexanal **4** with dynamic kinetic lipase-mediated resolution of 2-nitrocyclohexanol **5** (Scheme 2).

Therefore, use of a modified substrate, 2-methyl-2-nitrocyclohexanol **2**, was investigated, as it was envisaged that this would avoid base-mediated epimerisation at C2 due to the presence of the methyl moiety and, consequently, interconversion of the *cis*- and *trans*-2-methyl-2-nitrocyclohexanol (±)-**2a** and (±)-**2b** can only occur through ring opening and closing of the aldehyde 6-nitroheptanal **1**.

The bioresolution of an intramolecular nitroaldol reaction of 6-nitroheptanal **1** was investigated in a stepwise manner (Scheme 2). The first step in this study involved independent examination of the lipase-mediated kinetic resolution of the racemic *cis*- and *trans*-2-methyl-2-nitrocyclohexanols (±)-**2a** and (±)-**2b** identifying the most efficient lipase to perform this biotransformation enantioselectively and diastereoselectively. Ideally, for an efficient dynamic process, one enantiomer of either (±)-**2a** or (±)-**2b** would be efficiently and selectively acetylated. The alcohol substrates (±)-**2a** and (±)-**2b** were obtained by sodium borohydride reduction of 2-methyl-2-nitrocyclohexanone,[12,13] while subsequent acetylation with acetic anhydride in DCM with pyridine & catalytic DMAP gave



Scheme 3. Epimerisation pathway versus the reversible nitroaldol reactions.



Scheme 2. Stepwise investigation of the DKR of the intramolecular nitroaldol reaction through lipase catalysis.