Journal of Catalysis 361 (2018) 40–44

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Exploitation of differential electronic densities for the stereoselective reduction of ketones bearing a masked amino surrogate

Renta Jonathan Chew [a,b,*], Martin Wills [b,*]

[a] A*STAR Graduate Academy (A*GA), Agency for Science, Technology and Research (A*STAR), Singapore 138668, Singapore
[b] Department of Chemistry, University of Warwick, CV4 7AL, United Kingdom

ARTICLE INFO

Article history:
Received 27 September 2017
Revised 12 February 2018
Accepted 14 February 2018

Keywords:
Asymmetric reduction
Homogenous catalysis
Ruthenium
TsDPEN
Phthalimide
Amino alcohol

ABSTRACT

A tethered ruthenium-TsDPEN catalyst is employed for the facile catalytic asymmetric reduction of α-phthalimyl-α′-ketoethers under mild conditions. Leveraging exclusively on the contrasting electronic densities on the heteroatoms, a series of enantioenriched phthalimyl ether alcohols can be obtained in generally good stereoselectivities from this challenging class of substrate. Subsequent transformation into highly valuable chiral β-amino alcohols is demonstrated to take place without significant losses in yield and optical purity.

1. Introduction

The demand for enantiomerically enriched compounds notably in the pharmaceutical and agricultural industries has precipitated accelerated advancements in the field of asymmetric catalysis in recent years [1], the benefits of which include improved atom economy, reduced environmental impact and as an approach to circumvent the high cost and/or availability of chiral starting materials [2].

An integral component in a myriad of compounds, the chiral β-amino alcohol backbone can be found in pharmaceuticals [3], natural products [4] (Fig. 1) peptidomimetics [5] and perfumes [6]. Moreover, β-amino alcohols also function as resolving agents, ligands and auxiliaries in synthetic chemistry [7]. Yet, the conventional preparation of optically active β-amino alcohols is not straightforward with traditional methodologies requiring cumbersome multi-step synthetic transformations [4]. Having in recent years established a robust catalytic system employing tethered ruthenium-TsDPEN complexes (**1**) for the asymmetric reduction of several substrate classes, our group and others have made considerable progress with conventional ketones and imines [8]. The favourable electronic interaction (edge-face) between the electronically-rich groups in the substrate (aromatic, alkyne) and the electron deficient η^6-arene ring of the catalyst is critical for achieving excellent enantiocontrol (Scheme 1) [9]. As such, there exist an abundance of research on the asymmetric reduction of aromatic ketones and imines as they generally produce products with excellent enantioselectivities. Alkyl ketones bearing heteroatoms on the α-positions however have rarely been studied and in these cases, molecular hydrogen under high pressures is employed [10].

While the direct asymmetric reduction of α-amino-α'-ether ketones would afford the desired β-amino alcohols, it was apparent that this approach would produce undesirable optical purities since enantiocontrol is postulated to be controlled predominantly by the differential electronic densities of the heteroatoms flanking the keto group, although steric effects and dispersion forces also make significant contributions [9c]. Inspired by the concept of employing protecting-activating groups in the synthesis of carbohydrates [11], amino acids/peptides [12], macrocycles [13] as well as in hydrophosphination [14], the phthalimyl moiety was selected as a masked surrogate for the amino functionality owing to its low cost, stability and more importantly, its ease of deprotection and the ability to negate the high electronic density on the nitrogen atom. This protecting group has also been shown to be compatible in the ATH of acetophenone derivatives [15]. Herein, we report the facile asymmetric transfer hydrogenation (ATH) of α-phthalimyl-α′-ketoethers **2** under mild conditions and

* Corresponding authors at: Department of Chemistry, University of Warwick, CV4 7AL, United Kingdom (R.J. Chew).
E-mail addresses: chew0209@ntu.edu.sg, r.chew@warwick.ac.uk (R.J. Chew).

https://doi.org/10.1016/j.jcat.2018.02.014
0021-9517/

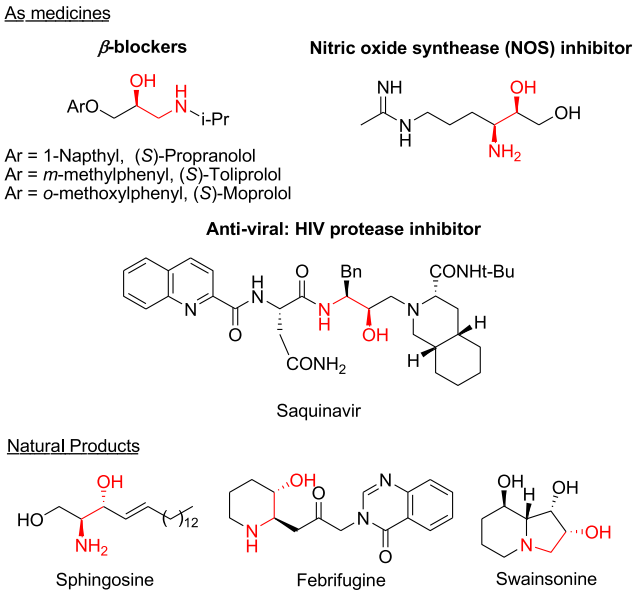
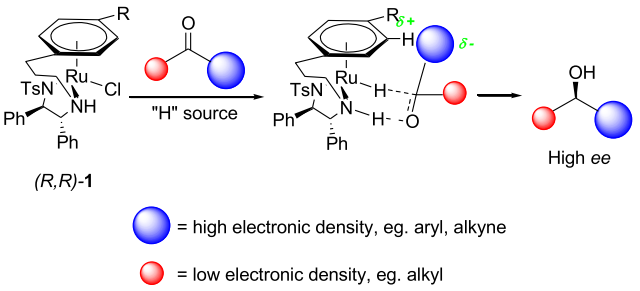


Fig. 1. Selected examples of medicines and natural products bearing the vicinal amino alcohol backbone.



Scheme 1. Favorable electronic directing effects affording products of excellent optical purities.

the subsequent transformation into chiral β-amino alcohols **3** (Scheme 2); the latter serving as invaluable building blocks towards prized compounds such as β-blockers as illustrated in Fig. 1.

2. Methods and materials

Analytical grade solvents were used directly without further purification as purchased from commercial sources: chloroform, acetone and tetrahydrofuran from VWR Chemicals; toluene, acetonitrile and concentrated sulphuric acid from Fischer Scientific; dichloromethane and 1,2-dichloroethane from Sigma Aldrich. Chiral tethered ruthenium catalyst (*R,R*)-**1a** supplied by Johnson Matthey and (*S*)-oxiranylanisole [97% sum of enantiomers] and AD-mix-α from Sigma Aldrich was used directly without further purification. Flash chromatography on silica was conducted on Sigma Aldrich silica gel (technical grade, pore size 60 Å, 230–400 mesh, 40–63 μm particle size). Room temperature is defined to be approximately 20 °C.

NMR spectra were recorded on Bruker Avance III HDF 400 and 500 spectrometers. ^{1}H NMR spectra chemical shifts were reported in δ ppm relative to chloroform (δ = 7.26 ppm) or tetramethylsilane (δ = 0.00 ppm). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as *J* value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ = 77.26 ppm). Optical rotations of optically active alcohols were measured in the specified solution using a 2 dm cell with an Optical Activity Ltd. AA-1000 polarimeter. Chiral HPLC was performed on a Hewlett Packard 1050 HPLC machine incorporating a Diacel CHIRAPAK® IA, IC or Diacel CHIRALCEL OD-H column.

Detailed procedures for the syntheses of all starting materials can be found in the Supplementary Material.

2.1. Ru/TsDPEN **1a** catalyzed asymmetric transfer hydrogenation of **2** and **5**

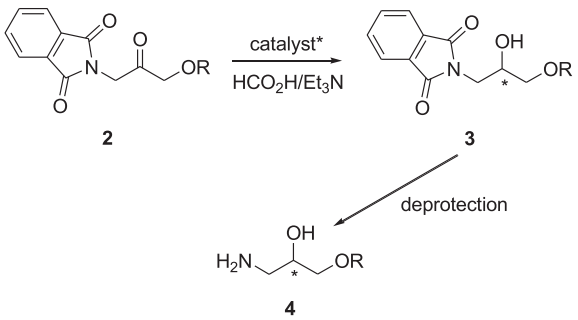
To a nitrogen flushed Schlenk tube was charged with ketone **2**,**5** (0.10–0.20 mmol) and catalyst (*R,R*)-**1a** (3 mol%) before the addition of equivalent volumes of chloroform and 5:2 formic acid/triethylamine solution (TEAF) such that the total concentration of the ketone is 1 M (unless otherwise stated). The reaction is allowed to stir overnight (>15 h) at room temperature (ca. 20 °C) before quenching with excess saturated sodium bicarbonate solution and subsequently extracting the mixture with ethyl acetate (2 × 3 mL). The combined organic layers were concentrated then purified by flash chromatography on silica to afford the desired chiral alcohols.

2.2. Deprotection of phthalimyl alcohol (*S*)-**3a**

Phthalimyl alcohol (*S*)-**3a** (294 mg, 0.99 mmol, 1 equiv.), hydrazine hydrate (0.29 mL, 5.94 mmol, 6 equiv.) was added to ethanol (40 mL) and the solution refluxed for 2 h. Consequently, the setup was cooled in ice water and white solids formed were filtered off by Celite and the cake washed with excess ethyl acetate. The filtrate was subject to solvent strip under reduced pressure and the residue purified by Kugelrohr distillation to afford (*S*)-**4a** (white solid, 142 mg, 86%).

3. Results and discussion

We began our study with the optimization of the ATH reaction using 2-(2-oxo-3-phenoxypropyl)isoindoline-1,3-dione **2a** as the prototypical substrate. A variety of conditions were examined ranging from the employed solvents, temperatures, catalyst (loading), formic acid-triethylamine molar ratio; the results are presented in Table 1. The catalyst loading was initially screened, with an increase in loading affording a slight improvement in enantiomeric excess (*ee*) (Table 1, entries 1–2). Subsequently, a range of solvents were studied and this study revealed that chloroform was the ideal solvent for the reaction (Table 1, entries 2–8). It was gratifying to note a considerable improvement of *ee* from 61 to 73% with the employment of a lowered temperature (Table 1, entries 2 and 9). Conversely, substituting the catalyst with a



Scheme 2. Synthetic pathway to optically active β-amino alcohols.