Exploitation of Differential Electronic Densities for the Stereoselective Reduction of Ketones Bearing a Masked Amino Surrogate

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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.

Keywords: asymmetric reduction; homogenous catalysis; ruthenium; TsDPEN; phthalimide; amino alcohol

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] (Figure 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

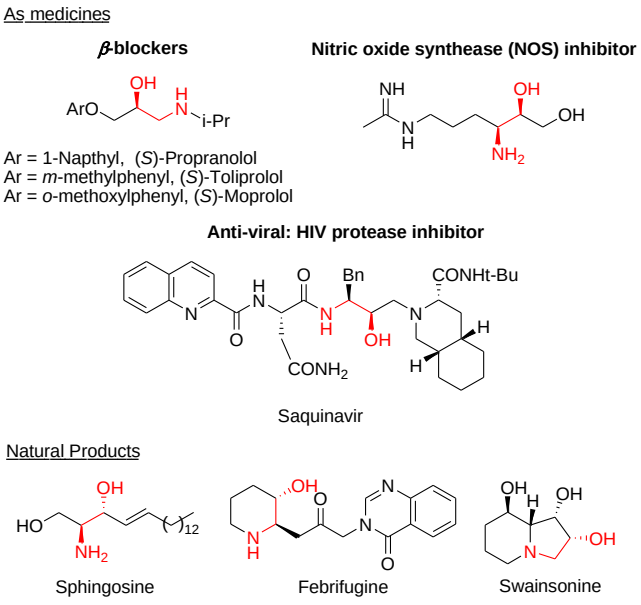
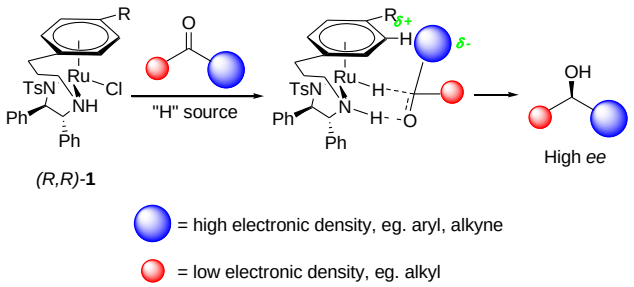


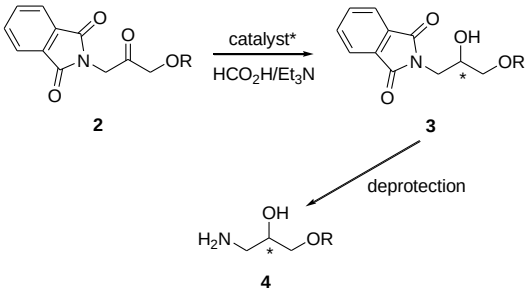
Figure 1. Selected examples of medicines and natural products bearing the vicinal amino alcohol backbone.



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

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 exists 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 a significant contribution.[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 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 Figure 1.



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

2. Experimental section

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 60Å, 230-400 mesh, 40-63 µm particle size). Room temperature is defined to be approximately 20 ºC.

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 Supporting Information.

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 1M (unless otherwise stated). Reaction is allowed to stir overnight (>15 hrs) at room temperature (ca. 20 ^{o}C) before quenching with excess saturated sodium bicarbonate solution and subsequently extracting the mixture with ethyl acetate (2 x 3 mL). The combined organic layers were concentrated then purified by flash chromatography on silica to afford the desired chiral alcohols.

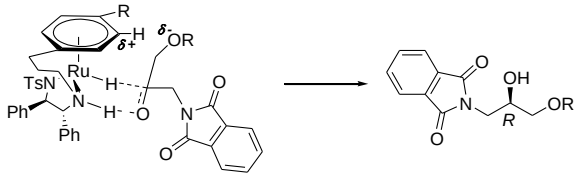
2.2 Deprotection of phthalimyl alcohol (*S*)-**3a**

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 hours. Consequently, the setup was cooled in ice water and white solid 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

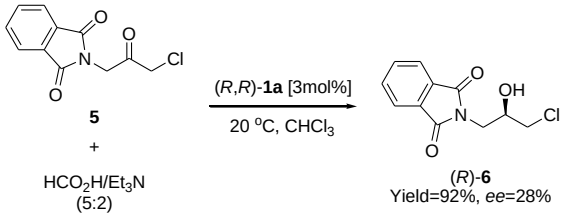
We began our study with the optimization of the ATH reaction using 2-(2-oxo-3-phenoxypropyl)isoindoline-1,3-dione **2a** as the prototypical substrate. A variety of conditions were examined ranging from the employed solvents, temperatures, catalyst (loading), formic acid-triethylamine molar ratio; the results are presented in Table 1. The catalyst loading was initially screened, with an increase in loading affording a slightly improved 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 2,9). Conversely, substituting the catalyst with a 4-methoxy analog **1b** or varying the formic acid/triethylamine ratio both produced less desirable outcomes (Table 1, entries 10-11). The absolute configuration of the newly formed chiral centre was established by the treatment of phthalimide with commercially available (*S*)-oxiranylanisole to give (*S*)-**3a.**[16] Subsequent comparison of HPLC data with that obtained in the ATH reactions confirmed our hypothesis that it is indeed the electronically richer oxygen heteroatom in **2a** interacting with the electron deficient η^6-arene ring of the catalyst (Scheme 3). This dominant directing effect thus affords optically enriched phthalimyl alcohol **3a** with the expected *R* configuration.

With the optimal conditions established, we screened a variety of substrates bearing various functionalities and the outcomes are illustrated in Table 2. Owing to the enhanced understanding of the catalytic mechanism whereby the catalyst prefers electronically richer elements adjacent to its aromatic ring, ketones bearing alkyl ethers (Table 2, entries 10-15) generally outperform aryl ether analogs (Table 2, entries 1-7) in terms of optical purities of the alcohol derivatives. On the contrary,



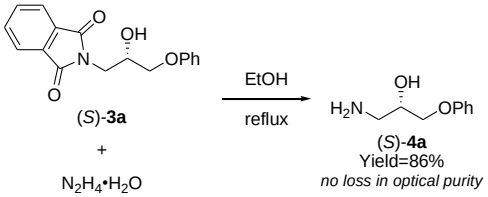
Scheme 3. Control of absolute configuration during reduction of substrate **2a**.

substituents containing electronic withdrawing moieties afforded products with significantly lower *ee*s (Table 2, entries 8-9). It is noteworthy that the 2-methoxy phenyl substrate (Table 2, entry 6) surpassed the *meta* and *para* counterparts (Table 2, entries 10-12), while the 2,6-dimethoxyphenyl analog afforded the best enantiomeric excess at 90% (Table 2, entry 7). While it is expected that the *para*-methoxy substrate **2d** would give a better enantioselectivity as compared to its *meta* analog **2e** aspredicted by Hammett's constants (σ_p = -0.27, σ_m = 0.12),[17] the enhanced enantioselectivities with *ortho* substituents (**2f-g**) could be postulated to be due to steric factors. In consideration of enantioenriched halohydrins being fundamental building blocks and target intermediates towards biologically active compounds,[18] we were keen on substituting the ether functionality in **2** with a halogen moiety, by virtue of the latter being a readily substituted group for further manipulations. Correspondingly, we studied the ATH of 2-(3-chloro-2-oxopropyl)isoindoline-1,3-dione **5** to give optically active chlorohydrin **6** (Scheme 4). In spite of the excellent yield obtained, enantiocontrol proved to be challenging, suggesting that a single chlorine atom cannot provide a directing effect similar to that of the alkoxy and aryloxy-groups in **2**. Despite the poor *ee*, to the best of our knowledge, this is one of the few reported examples of the asymmetric reduction of ketones bearing the 1-chloro-2-propanone backbone. Asymmetric transfer hydrogenation, in good yield and *ee* of structurally related *N*-protected (3*S*)-3-amino-1-chloro-4-phenyl-2-butanones with analogous Rh(III) complexes has been reported[19] however the majority of the studies primarily involving α-chloromethyl aromatic ketones as substrates.[20]



Scheme 4. Preparation of optically active halohydrin via ATH.

To demonstrate the versatility of the phthalimyl moiety as an excellent surrogate for the amino group, enantiopure (*S*)-**3a** was treated with hydrazine to give amino alcohol (*S*)-**4a** in excellent yield with no observable loss in enantiomeric purities (Scheme 5).[16] Derivatives of compound **4** can be further converted into a series of β-blockers (Figure 1), thus offering an attractive alternative synthetic path for their preparation.



Scheme 5. Facile deprotection of phthalimyl alcohol with no observable loss in optical purity.

4. Conclusions

In conclusion, the challenging catalytic asymmetric transfer hydrogenation of α-phthalimyl-α'-ketoethers has been achieved under mild conditions, affording phthalimyl alcohols in good to excellent yields with a range of enantiomeric excesses. The effects of differential electronic densities on the heteroatoms in influencing enantioselectivity are elucidated in this study, contributing towards an improved understanding to the mechanisms of reduction by tethered Ru(II) catalysts. More importantly,

the obtained alcohols can be readily deprotected to give optically active amino alcohols which are invaluable building blocks to a variety of prized compounds.

Author Contributions

The manuscript was written through contributions from both authors. Both authors have given approval to the final version of the manuscript. The project was conceived and conducted by R. J. Chew and the manuscript written and proofread by R. J. Chew and M. Wills.

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Notes

The authors declare not competing financial interests.

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Supplementary Material

Supporting information can be found in the online version at http://dx.doi.org/10.1016/j.jcat.xxxxxxx

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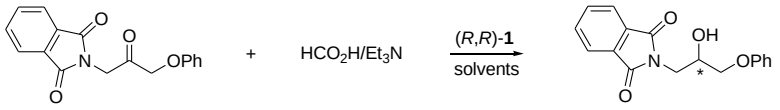
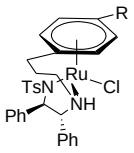
Table 1. Optimization of reaction conditions for the catalytic ATH of 2-(2-oxo-3-phenoxypropyl)isoindoline-1,3-dione **2a**[a]



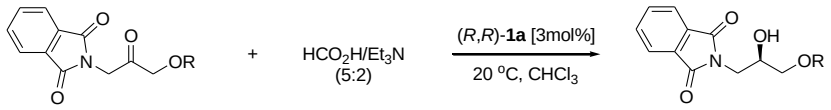


(R,R)-**1**
R=H, **1a**
R=OMe, **1b**

Entry	Catalyst / Loading (mol%)	Temperature (°C)	HCO_2H:Et_3N[b]	Solvent	Yield[c] (%)	*ee*[d] (%)
1	**1a** / 1	40	5:2	$CHCl_3$	77	59
2	**1a** / 3	40	5:2	$CHCl_3$	72	61
3	**1a** / 5	40	5:2	THF	48	48
4	**1a** / 5	40	5:2	toluene	51	52
5	**1a** / 3	40	5:2	MeCN	78	50
6	**1a** / 3	40	5:2	$MeNO_2$	93	55
7	**1a** / 3	40	5:2	DCM	71	54
8	**1a** / 3	40	5:2	1,2-EDC	91	57
9[e]	**1a** / 3	rt (20)	5:2	$CHCl_3$	91	73
10[e]	**1a** / 3	rt (20)	3:2	$CHCl_3$	82	57
11[e]	**1b** / 3	rt (20)	5:2	$CHCl_3$	90	56

[a] Reaction conditions: ca. 0.15 mmol 2a, [2a]=1M (in equal volumes of formic acid/triethylamine solution and added solvent), >15hrs reaction time; [b] Molar ratio; [c] Isolated yield; [d] Enantiomeric excess as determined by HPLC; [e] Excess solvents are added: [2a]=0.50M.

Table 2. Substrate table for the catalytic ATH of *α*-phthalimyl-*α*'-ketoethers **2**[a]



Entry	Substrate	R	Product	Yield[b] (%)	*ee*[c] (%)
1[d]	**2a**	phenyl	**3a**	91	73
2[e]	**2b**	2-napthyl	**3b**	92	76
3	**2c**	4-MeC_6H_4	**3c**	95	78
4	**2d**	4-$MeOC_6H_4$	**3d**	88	75
5[d]	**2e**	3-$MeOC_6H_4$	**3e**	88	71
6	**2f**	2-$MeOC_6H_4$	**3f**	92	82
7	**2g**	2,6-$MeOC_6H_3$	**3g**	93	90
8[d]	**2h**	4-PhC_6H_4	**3h**	89	66
9[f]	**2i**	4-BrC_6H_4	**3i**	95	58
10	**2j**	methyl	**3j**	90	77
11	**2k**	isopropyl	**3k**	76	79
12[d]	**2l**	allyl	**3l**	84	78
13[d]	**2m**	propargyl	**3m**	89	81
14[d]	**2n**	benzyl	**3n**	99	76
15[d]	**2o**	furfuryl	**3o**	86	84

[a] Reaction conditions: *ca.* 0.10-0.20 mmol **2**, [**2**]=1M (in equal volumes of formic acid/triethylamine solution and added solvent), >15hrs reaction time; [b] Isolated yield; [c] Enantiomeric excess as determined by HPLC; Due to poor solubility of the substrate, excess solvents are added: [d] [**2**]=0.50M, [e] [**2**]=0.067M, [f] [**2**]=0.25M