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Biocatalytic and chemocatalytic approaches to the highly stereoselective 1,2-reduction of an α,β-unsaturated ketone

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Abstract—Two methods are reported for synthesizing a chiral allylic alcohol from the corresponding racemic α,β-unsaturated ketone. Transition metal-based transfer hydrogenation provides the desired allylic alcohol in high enantiomeric purity but low diastereomeric excess. In contrast, an enzymatic dynamic kinetic reduction proceeds with high diastereoselectivity and enantioselectivity.

1. Introduction

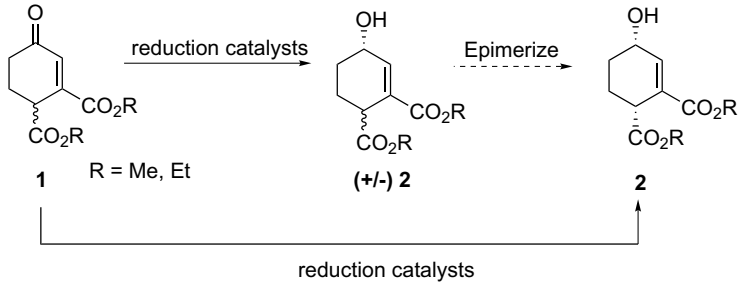
Chiral allylic alcohols are versatile synthetic precursors for building blocks in natural and non-natural compounds.[1] Numerous useful methods have been reported for their synthesis.[2–7] In the context of a drug development program, an efficient method for synthesizing chiral alcohol **2** was required (Scheme 1). We envisioned accomplishing this via an asymmetric reduction of the racemic α,β-unsaturated ketone **1** either via asymmetric reduction of the ketone, followed by epimerization, or a dynamic kinetic reduction to produce **2** directly.[8] While reductions of enones[9,10] and specifically 2-cyclohexenones[11–14] have been described, the reduction of **1** poses the additional challenge of having a proximal racemic center which can potentially have competing directing effects on the asymmetric reduction thereby lowering the overall yield.[15–23]

Herein, we describe our parallel efforts to effect the transformations highlighted in Scheme 1 using both an enantioselective transfer hydrogenation and an enzyme mediated reduction. These reactions are characterized by their high degree of stereoselectivity and chemoselectivity.

2. Results and discussion

2.1. Chemocatalytic reduction of 1

Initial screening efforts focused on identifying catalysts which employed gaseous dihydrogen as a reductant.[20,24,25]



Scheme 1. Synthetic routes to allylic alcohol **2** include asymmetric reduction of the ketone followed by epimerization or a dynamic kinetic reduction.

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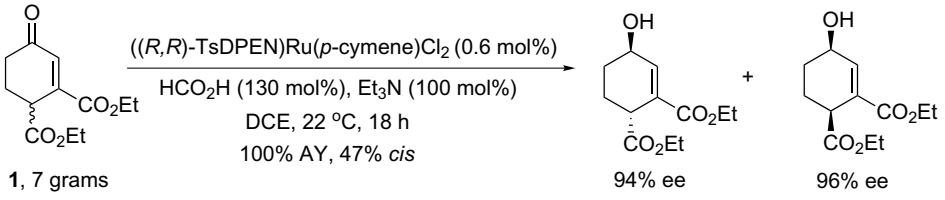
In particular, (xylBINAP)(DAIPEN)$RuCl_2$ and ligand/$[(COD)IrCl]_2$ (ligand = SLJ002-1, TMBTP) were examined against ketone **1**. With ruthenium, poor enantioselectivity (~30–50% ee) and no diastereoselectivity were obtained. In addition, substantial substrate decomposition was also observed—likely a result of the base added to activate the catalyst (K_2CO_3 and KO^{t}Bu). In contrast to ruthenium, little substrate degradation occurred with the iridium catalysts; however, the iridium catalyzed hydrogenations proceeded in low enantioselectivities (<25% ee) and were plagued with unwanted 1,4 reduction of the olefin. Based on these preliminary results, continued screening of this class of catalysts was discontinued and subsequent emphasis was placed on transfer hydrogenation catalysts.

Transfer hydrogenation catalysts employing ruthenium, rhodium, and iridium were examined.[2,26–29] The results from this initial screen are presented in Table 1. Gratifyingly, all the catalysts examined proceeded with high enantioselectivity when TsDPEN (*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine) was employed as the chiral ligand. It is important to note that 1,4-reduction was not observed (^{1}H NMR spectroscopy and HPLC). Under the conditions examined, little diastereoselectivity was obtained. Interestingly, the racemic stereogenic center in **1** had little influence on the transfer hydrogenation of ketone; that is, this reduction is primarily catalyst controlled. Based upon our subsequent epimerization attempts (vide infra), the diastereomeric ratio is likely not changed due to epimerization after the transfer hydrogenation.

Due to the project time limit, subsequent optimization efforts focused on (TsDPEN)(*p*-cymene)$RuCl_2$. A total of six solvents and three different catalyst loadings were examined. The results from this screen are presented in Table 1. Surprisingly, at the catalyst loadings examined, the solvent had little impact on reaction rate, enantioselectivity, diastereoselectivity, and 1,4-reduction. In all cases, both diastereomers were produced in high enantiomeric excesses. In order to streamline downstream processing, subsequent reactions were performed in dichloroethane. With the optimized conditions, the transfer hydrogenation was performed on a 7 g scale and proceeded in high yield and enantiomeric excess (Eq. 1). It should be noted that the methyl and ethyl esters behaved similarly with (TsDPEN)(*p*-cymene)$RuCl_2$ giving nearly identical results (Table 1, entries 1 and 9).

As described in the introduction, we ultimately sought to prepare **2** as a single enantiomer via epimerization of the sp^3 center alpha to the carbonyl functionality. In both THF and toluene, strong bases such as lithium tetramethylpiperidine and potassium *t*-butoxide were ineffective reagents for effecting this conversion giving substantial decomposition and no epimerization. Attempts with transition metal isomerization catalysts such as $Rh(Cl)(PPh_3)_3$ and $(PPh_3)_3Ru(H)Cl$ were also unsuccessful.



(1)

The transfer hydrogenation provided a quick way to generate multiple grams of substrate for evaluation of downstream chemistry; however, the inability to epimerize **2** ultimately ruled out its implementation in our synthetic design. During the course of our chemocatalytic development, an enzymatic reduction, as described below, was identified which produced **2** in both high enantioselectivity and diastereoselectivity. Consequently, development efforts focused on elaborating and optimizing this lead.

Table 1. Transfer hydrogenation results for substrate **1** (R = Et, Me)[a]

Entry	R	Metal[b]	mol % Catalyst[c]	Solvent	% *cis*	% ee *cis*[d]	% ee *trans*[d]
1	Et	Ru	0.5	Dichloroethane	50	95	96
2	Et	Ru	0.5	*N*,*N*-Dimethylformamide	51	93	95
3	Et	Ru	0.5	2-Propanol	52	97	97
4	Et	Ru	0.5	Toluene	54	96	96
5	Et	Ru	0.5	Ethanol	56	98	97
6	Et	Ru	0.5	Isopropyl acetate	55	95	96
7	Et	Ru	0.5	*tert*-Butylmethyl ether	55	95	96
8	Et	Ru	0.5	Tetrahydrofuran	55	94	95
9	Me	Ru	0.2	Dichloroethane	48	94	95
10	Et	Rh	5.0	Dichloroethane	45	98	97
11	Et	Ir	5.0	Dichloroethane	41	95	97

[a] 20 mg **1** per reaction in 300 μL solvent, 100 mol % triethylamine, 130 mol % formic acid, 22 °C, 15 h, >99 HPLC area percent conversion was obtained.
[b] Metal pre-cursor, Ru = $[(p\text{-cymene})RuCl_2]_2$; Rh = $[Cp * RhCl_2]_2$; Ir = $[Cp * IrCl_2]_2$.
[c] Catalyst = (metal)(*R*,*R*-TsDPEN)(*p*-cymene)Cl_2 (*R*,*R*-TsDPEN = (1*R*,2*R*)-(−)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine).
[d] All reductions give the (*R*)-enantiomer. Use of *S*,*S*-TsDPEN gives the (*S*)-enantiomer. Stereochemical assignments are based on literature precendence.[27,30]

2.2. Biocatalytic reduction of 1

Biocatalytic reductions of α,β-unsaturated ketones have been reported with excellent chemoselectivity for the reduction of the carbonyl functionality by employing either whole cells with redox-enzymatic activity or isolated alcohol dehydrogenases.[22,31–39] To the best of our knowledge, these reported reductions have not simultaneously included a racemization step aimed at achieving 100% theoretical yield of enantiomerically pure material. We focused on isolated enzymes in order to avoid any interfering competitive reduction of the conjugated carbon–carbon bond as observed for some whole cell systems.[40–50] The results from a screen of our in house library of commercially available ketoreductases and alcohol dehydrogenases in the presence of excess NAD(P)H are presented in Table 2.

This initial screen was promising in that good to excellent enantioselectivities and diastereoselectivities were observed (Table 2). The group of enzymes including KRED102, ADH Cp, and ADH Re (Table 2, entries 2, 21, and 22) displayed catalyst-controlled reductions similar to the chemocatalytic transfer hydrogenation approach, yielding alcohol **2** in high enantioselectivity at the hydroxy functionality [>90% ee (*S*) for both *cis* and *trans*] but no diastereoselectivity (~50% *cis*). A second set of enzymes including KRED118 and KRED121 (Table 2, entries 13 and 16) demonstrated substrate-controlled reduction where the enzyme recognized the conformation of the chiral ester moiety and directed the ketone reduction in a *syn* fashion. As a result, *rac*-ketone **1** was reduced with high diastereoselectivity (99% *cis*) but no enantioselectivity (<5% ee). Finally, the third group of biocatalysts including KRED108, KRED116, KRED117, and KRED120 (Table 2, entries 5, 11, 12, and 15), displayed combined catalyst-controlled and substrate-controlled mechanisms, reducing racemic ketone **1** to chiral *cis*-alcohol **2** in good enantioselectivity (>75% ee) and excellent diastereoselectivity (99% *cis*). These enzymes produced the chiral alcohol stereocenter in a predominantly (*S*)-configuration with KRED108 giving 82% ee (*S*) in the screen (Table 2, entry 5). To obtain this result, only one ester enantiomer is selectively reduced at the ketone functionality, theoretically limiting the reduction to 50% conversion. With KRED108, KRED116, and KRED117 (Table 2, entries 5, 11, and 12), greater than 50% conversion is obtained which necessarily means that racemization at the ester moiety was occurring under the mild biocatalysis reaction conditions (pH 6.5). Thus, the enzyme-mediated dynamic kinetic reduction provides a facile method for obtaining enantiopure material from racemic starting material.

Table 2. Enzymatic ketone reduction screening results for substrate **1** (R = Et)[a]

Entry	R	Enzyme[b]	Area % conversion	% *cis*[c]	% ee *cis*[d]	% ee *trans*[d]
1	Et	KRED101	74	83	1	5(*S*)
2	Et	KRED102	76	50	91(*S*)	99(*S*)
3	Et	KRED103	58	74	99(*S*)	99(*S*)
4	Et	KRED106	27	33	99(*S*)	99(*S*)
5	Et	KRED108	73	99	82(*S*)	—
6	Et	KRED111	82	89	1	99(*S*)
7	Et	KRED112	78	86	2	14(*R*)
8	Et	KRED113	81	87	6(*R*)	27(*R*)
9	Et	KRED114	81	91	1	33(*R*)
10	Et	KRED115	81	90	0	40(*R*)
11	Et	KRED116	75	99	80(*S*)	—
12	Et	KRED117	74	99	76(*S*)	—
13	Et	KRED118	83	99	4	—
14	Et	KRED119	80	99	40(*S*)	—
15	Et	KRED120	56	99	86(*S*)	—
16	Et	KRED121	70	99	0	—
17	Et	KRED123	81	91	1	78(*R*)
18	Et	KRED124	70	41	66(*S*)	99(*S*)
19	Et	ADH Lb	37	98	52(*R*)	—
20	Et	ADH Lk	44	89	48(*R*)	99(*S*)
21	Et	ADH Cp	27	45	99(*S*)	99(*S*)
22	Et	ADH Re	46	50	99(*S*)	99(*S*)

[a] 2 mg **1** per reaction in 1 mL 0.5 M KH_2PO_4 pH 6.5, 5 vol % MeOH, 1 mg lyophilized enzyme preparation (KRED101-127, BYADH) or 10 μL liquid enzyme preparation, respectively, 10 mg NAD(P)H. 30 °C, 18 h.

[b] KRED = ketoreductase, ADH = alcohol dehydrogenase, Lb = *Lactobacillus brevis*, Lk = *Lactobacillus kefir*, Cp = *Candida parapsilosis*, Re = *Rhodococcus erythropolis*.

[c] KRED104, 105, 107, 109, 110, 122, 125, 126, 127; horse liver alcohol dehydrogenase, baker's yeast alcohol dehydrogenase, and *C. bodinii* alcohol dehydrogenase all gave <25% conversion.

[d] Stereochemical assignments were made based on comparison to results shown in Table 1.

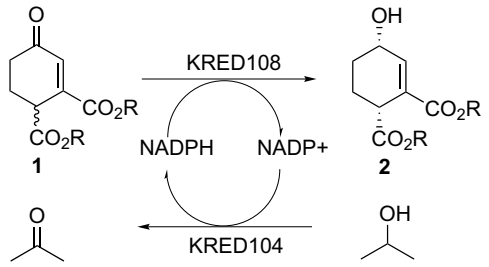
After identifying KRED108 as a potential lead, we focused on measuring the inherent reaction enantiomeric excess at 100% conversion since the result from our screen only went to 73% conversion. This was accomplished by running the reduction in the presence of excess NADPH (3.75 mol equiv vs 1.5 mol equiv for screening). Complete conversion to **2** occurred but the enantiomeric excess was only 60% (*S*) (Table 3, entry 1). We hypothesized that under these conditions the enzymatic reduction rate was faster and as a result the reduction rate of the slower ketone enantiomer was increased relative to the racemization of **1**, making the reaction less selective. We then investigated improving the selectivity of the reduction by substrate modification. Surprisingly, a slight change in the ester moiety of **1** to the less sterically demanding methyl ester produced the chiral alcohol stereocenter in 95% enantiomeric excess (*S*) with near perfect diastereoselectivity (Table 3, entry 2). The results from the substrate modification could likely be a result of the improved racemization rate of methyl versus ethyl ester **1** consistent with our hypothesis, or alternatively, improved enzyme/substrate binding interactions. It should also be noted that **1** can be viewed as a vinylogous keto-ester. Conjugation between

Table 3. Improvement of the stereoselectivity of KRED108 reducing derivatives of substrate **1**

Entry	R	Enzyme	Area % conversion	% *cis*	% ee *cis*
1[a]	Et	KRED108	97	99	60(*S*)
2[a,b]	Me	KRED108	97	99	95(*S*)

[a] 100 mg **1** per reaction in 15 mL 0.5 M KH_2PO_4 pH 6.5, 5 vol % methanol, 15 mg KRED108, 1.3 g NADPH, 35 °C, 4 h.

[b] 100 mg **1** per reaction in 10 mL 0.5 M KH_2PO_4 pH 6.5, 5 vol % 2-propanol, 30 mg KRED108, 30 mg $NADP^+$, and 120 mg KRED104, 35 °C, 18 h.



Scheme 2. Enzymatic asymmetric reduction of ketone **1** with KRED108 including NADPH cofactor recycling system using KRED104/2-propanol.

ketone and ester functionalities likely significantly effects its reactivity.

Since the result with the methyl ester derivative of **1** met the target requirement regarding selectivity, we investigated cofactor recycling systems to decrease NADPH usage and to drive the equilibrium further toward production of the alcohol **2** by keeping the NADPH to NADP ratio high. Our first choice was to recycle NADPH using glucose/glucose dehydrogenase (GDH) according to a coupled enzyme approach.[51] Unexpectedly, GDH displayed activity on ketone **1** and non-selectively produced alcohol **2**, causing a loss of diastereoselectivity (*cis*/*trans* 2/1) and likely enantiomeric excess. Consequently, we decided to use KRED104, an enzyme which was only slightly active on **1** during the initial screen (Table 2, footnote C, 4 area% conversion), for NADPH recycling using 2-propanol as hydrogen source (Scheme 2). Since 2-propanol also served as co-solvent to enhance the solubility of the substrate **1**, we were able to charge ketone **1** as a stock solution in 2-propanol for the recycling system.

The process employing the KRED104/2-propanol cofactor recycling system behaved as expected and provided chiral alcohol **2** (R = Me) with the same diastereo- and enantiopurities (Table 3, entry 2b) as that observed when NADPH was used stoichiometrically. The process was demonstrated using the high catalyst loading of 3 mg/mL KRED108 and 12 mg/mL KRED104 to ensure quantitative reduction of **1** overnight, as described in Section 4. We recognize that these are unoptimized conditions and would expect process development to significantly reduce the catalyst loading.

3. Conclusion

The discovery and development of two approaches to the highly stereoselective reductions of ketone **1** to produce a chiral allylic alcohol are reported. With the chemocatalytic approach, the alcohol is produced in high enantioselectivities with little diastereomeric differentiation. The enzymatic reduction of **1** resulted in *both* high enantio- and diastereoselectivities. This combined dynamic kinetic racemization/reduction is a powerful method for producing highly stereoenriched material in excellent yields from a readily available racemic ketone.

4. Experimental

4.1. Materials

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. For the transfer hydrogenation reactions, all solvents were sparged with nitrogen for 30 min prior to use. KRED101 to KRED127, GDH, and NAD(P)(H) were purchased from Biocatalytics, Inc. HLADH and BYADH were obtained from Sigma. ADH Lb, ADH Lk, ADH Cb, ADH Cp, and ADH Re were purchased from X-Zyme GmbH. Compound **1** was prepared according to literature procedures.[52] Racemic standard **2** (R = Me, Et) was prepared via reduction of **1** with sodium borohydride. Conversion and diastereomeric excess was determined on an Agilent HPLC system using a Zorbax eclipse XDB C18 column (4.6 × 150 mm) at a gradient from 35/65 MeCN/water (0.1% H_3PO_4) to 95/5 over 14 min at 1 mL/min, rt, 210 nm. Enantiomeric excess determined with a Berger SFC system employing a tandem Chiralpak OD (250 × 4.6 mm)-Chiralpak OB (250 × 4.6 mm), isocratic 3% 2-propanol/CO_2 @ 2 mL/min, 200 bar, 35 °C, 30 min. Alternatively, product **2** enantiomeric excess could be measured by chiral gas chromatography: Agilent GC system, Varian Chiralsil-Dex Cb (25 m × 0.32 mm, 0.25 μm film thickness) ramp from 70 °C to 190 °C @ 2 °C/min, ramp to 200 °C @ 1 °C/min, hold for 10 min, average velocity 39 cm/s.

4.2. Transfer hydrogenation of 1 (R = Et)

In an inert atmospheres glove box, a vial was charged with [(*p*-cymene)$RuCl_2$]$_2$ (54 mg, 0.09 mmol), (*R*,*R*)-TsDPEN (64 mg, 0.18 mmol), dichloroethane (5 mL) and a stirbar. After 5 min, this solution was transferred to a round bottom flask containing **1** (7.0 g, 29 mmol), dichloroethane (75 mL), and a stirbar. To this were added a dichloroethane (30 mL) solution of triethylamine (4.1 mL, 29 mmol) and formic acid (1.4 mL, 38 mmol). The transfer hydrogenation reactions were typically complete in ~6 h; however, this reaction was aged overnight (18 h), after which time the reaction was removed from the glovebox and the solvent removed under reduced pressure to give **2** as a light yellow oil (7.03 g, 100% yield). An identical procedure was followed for **1** (R = Me). ^{1}H NMR for R = Et (*cis*, *trans* mixture) ^{1}H NMR (399.9 MHz, DMSO-d_6, 27 °C) δ 6.80 (d, 1H, J = 3.2 Hz), 5.21 (br s, 2H), 4.05 (m, 2H), 4.01 (m, 4H), 3.29 (m, 1H), 3.25 (m, 1H), 1.77 (m, 2H), 1.76 (m, 1H), 1.32 (m, 1H), 1.11 (m, 6H). ^{1}H NMR for R = Me (*cis*, *trans* mixture) ^{1}H NMR (399.9 MHz, DMSO-d_6, 27 °C) δ 6.84 (s, 2H), 5.12 (br d, 2H, J = 12 Hz), 4.15 (br s, 2H), 3.62 (s, 6H), 3.57 (s, 3H), 3.55 (s, 3H), 3.31 (m, 2H), 1.99 (m, 1H), 1.87 (m, 1H), 1.77 (m, 1H), 1.75 (m, 2H), 1.55 (m, 1H), 1.36 (m, 2H).

4.3. Screening conditions for the enzymatic reduction of 1 with excess NAD(P)H

A lyophilized enzyme (1 mg) or a liquid enzyme preparation (10 μL) was dissolved in buffer (0.5 mL or 0.49 mL 0.5 M KH_2PO_4, pH 6.5) and combined with a solution of

NADPH (12 μmoles) in KH_2PO_4 buffer (0.45 mL, 0.5 M, pH 6.5). A solution of **1** (2 mg, 8 μmoles) in methanol (0.05 mL) was added. The reaction was carried out in an incubator at 30 °C for 18 h.

4.4. Enzymatic reduction of 1 with excess NADPH

Ketoreductase KRED108 (15 mg) was dissolved in buffer (14 mL, 0.5 M KH_2PO_4, pH 6.5) and combined with a solution of NADPH (1.3 g, 1.5 mmoles) in KH_2PO_4 buffer (0.5 mL, 0.5 M, pH 6.5). To this was added a solution of **1** (100 mg, 0.4 mmoles) in methanol (0.5 mL). The reaction was carried out in an incubator at 35 °C for 4 h. Product **2** was extracted into ethyl acetate and concentrated under vacuum. **2** (R = Et): 76% isolated yield, 99% de *cis*, 60% ee (*S*) at COH. **2** (R = Me): 89% isolated yield, 99% de *cis*, 95% ee (*S*). ^{1}H NMR (399.9 MHz, acetonitrile-d_3, 27 °C) δ 6.95 (s, 1H), 4.30 (m, 1H), 3.65 (s, 3H), 3.42 (m, 1H), 2.45 (m, 2H), 2.35 (m, 2H), 2.1 (m, 2H) 1.98 (m, 1H). ^{13}C NMR (125 MHz, THF-d_8, 27 °C) δ = 24.8, 28.9, 41.0, 52.7, 52.8, 66.3, 130.0, 144.4, 167.6, 175.1 ppm.

4.5. Enzymatic reduction of 1 including NADPH-cofactor recycling

Ketoreductase KRED108 (30 mg) was dissolved in KH_2PO_4 buffer (4.5 mL, 0.5 M, pH 6.5) and combined with a solution of ketoreductase KRED104 (120 mg) and $NADP^+$ (30 mg) in KH_2PO_4 buffer (5 mL, 0.5 M, pH 6.5). To this was charged a solution of **1** (100 mg, 0.47 mmoles) in 2-propanol (0.5 mL). The reaction was carried out in an incubator at 35 °C for 12 h. Product **2** was extracted into ethyl acetate and concentrated under vacuum. **2** (R = Me): 94% isolated yield 99% de *cis*, 95% ee (*S*) at COH.

Acknowledgements

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