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Enzyme-Catalyzed Enantioselective Diaryl Ketone Reductions

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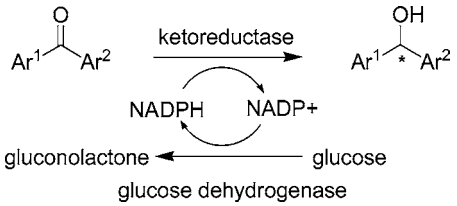
ABSTRACT



The synthesis of diarylmethanols via the reduction of a range of substituted benzophenone and benzoylpyridine derivatives with ketoreductase enzymes (KREDs) has afforded chiral products with high yield (>90%) and ee (up to >99%). Ortho, meta, and para substitutions with a variety of electron-donating, electron-withdrawing, and halogen groups were examined. Substitution at the ortho position and/or highly electronically dissymmetric molecules were not required for good selectivity, as is the case with conventional chemical catalyst reductions.

The need to deliver optically pure substances for the pharmaceutical industry, combined with the common difficulties and costs of separating two enantiomers, has led to new stereoselective synthesis methods for the production of chiral intermediates in drug synthesis.[1]

The formation of chiral diarylmethanols is of particular interest since intermediates of this type are important building blocks in the synthesis of pharmaceutically important molecules including antihistaminic, anaesthetic, diuretic, antidepressive, antiarrhythmic, and anticholinergic compounds.[2−4]

Catalytic, asymmetric syntheses of diarylmethanols typically involve either the addition of aryl nucleophiles to aromatic aldehydes or the reduction of the corresponding diaryl ketones.[2] This paper will focus on enzymatic strategies for the production of diarylmethanols via diaryl ketone reduction, and their advantages compared to classical chemical catalytic methods.

The addition of aryl nucleophiles to aromatic aldehydes has been demonstrated to form several diarylmethanols with high selectivity; however, these reactions exhibit serious drawbacks in their potential for large-scale industrial use. Diphenylzinc, the most common aryl donor, is expensive, not readily available for large-scale use, and limited to transferring a nonsubstituted phenyl group to the aldehyde. The use of boronic acid aryl sources enabled the transfer of substituted aryl rings, but arylboronic acid protocols typically require a large excess of diethylzinc (7 equiv) and additives such as dimethylpolyethyleneglycol (DiMPEG) to achieve good selectivity. Finally, nonselective, noncatalytic background aryl addition can lead to low product ee. This is typically combatted by increasing catalyst loading and reducing reaction temperature.

The stereoselective reduction of inexpensive prochiral ketones to their corresponding alcohols is potentially one of the most useful ways of introducing chirality in a molecule. However, the enantioselective reduction of diaryl ketones has proven to be a significant challenge, as chemical catalysts have an extremely limited substrate range.[5,6] There are a few

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examples of highly selective diaryl ketone reductions involving hydrogenation or CBS reduction.[7−9] The highly enantioselective (>95% ee) reduction of select benzophenones has been demonstrated by using lithium aluminum hydride−chiral amino alcohol complexes,[10,11] *B*-chlorodiisopinocampheylborane,[12] oxazaborolidine,[13] and chiral diphosphine/diamine Ru complexes.[14] These types of chemically catalyzed diaryl ketone reductions rely on both electronic and steric effects to determine the degree of enantioselectivity. Their limitation lies in the fact that their substrates must either be highly electronically dissymmetric or have an ortho-substituted aryl group to achieve good selectivity. For example, the highly selective CBS reduction of ketone **1** takes advantage of the electron-donating and -accepting groups on either end of the molecule, while the reduction of ketone **2** demonstrates that the presence of an ortho substituent on one of the aryl groups provides sufficient steric effect for excellent selectivity. Simple meta and para substitutions resulted in moderate to no selectivity.[13,15]

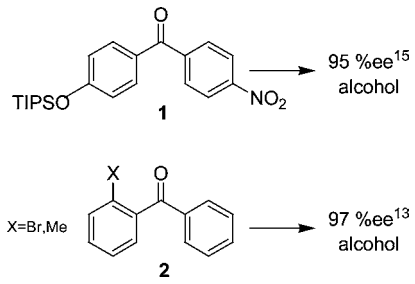

Figure 1. Highly selective CBS reduction of select diaryl ketones

Biological catalysts in the form of whole cells have been shown to be extremely stereoselective in the reduction of some diaryl ketones that are difficult to reduce with chemical catalysts. Immobilized baker's yeast catalyzed the reduction of 2-benzoylpyridine in hexane to afford the alcohol with high optical purity (96% ee).[16] Selected strains from *Hansenula nonfermentans*, *santamariae*, *ernobii*, *Rhodosporidium toruloides*, *Candida bombi*, and *sorbophila* have also been shown to reduce diaryl ketones with high selectivity, producing alcohol product with >95% ee.[5] Disadvantages of whole cell biocatalytic systems are that they are typically run at low substrate loading (1 g/L) and many times lead to low product yield (~10%) due to difficulties in isolating the product away from the cells.[17]

Isolated ketoreductase enzymes have been demonstrated to be highly selective catalysts for the reduction of a wide range of ketones.[18] Additionally, many of these enzymes are readily available and have been used to economically deliver kilogram quantities of chiral intermediates with excellent ee (>99%) and isolated yield (>90%).[19,20]

This work demonstrates a practical procedure for the enantioselective reduction of diaryl ketones by using isolated enzymes and its general application to a broad range of substrates (Scheme 1). Each of the enzymes used for these transformations required NADPH cofactor as the hydride source, so an NADPH recycling system was put in place by using glucose and a co-enzyme glucose dehydrogenase (GDH) to regenerate the reduced form of the cofactor. The presence of the recycle system also provides the driving force to take these reactions to completion. Additionally, all of the enzymes used for these transformations are readily and economically available in large quantities from commercial sources (Biocatalytics Inc.).

Scheme 1. KRED-Catalyzed Enantioselective Diaryl Ketone Reduction

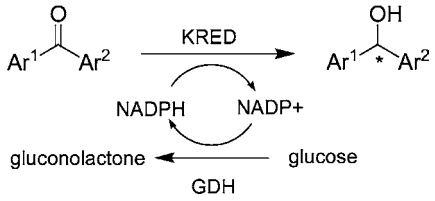

Figure 2 shows the range of diaryl ketone substrates that were screened against our in-house library of commercially available ketoreductases (KREDs). The range of substrates includes ortho-, meta-, and para-substituted benzophenones as well as several benzoylpyridines. Aryl substitutions included electron-donating, electron-withdrawing, and halogen substituents. Table 1 shows the results of the enzyme catalyst screen with the highest ee obtained for each enantiomer of the diarylmethanol products along with the corresponding enzyme catalysts. Isolated yields are also identified for select reactions that were demonstrated at the 1 g scale.

Generally, ortho-substituted substrates afforded greater alcohol product ee than their meta- and para-substituted counterparts. This trend was observed in methyl (**3a**, **3b**, **3c**), hydroxy-, (**3f**, **3g**, **3h**), amino- (**3i**, **3j**), and chloro- (**3*l***, **3m**,

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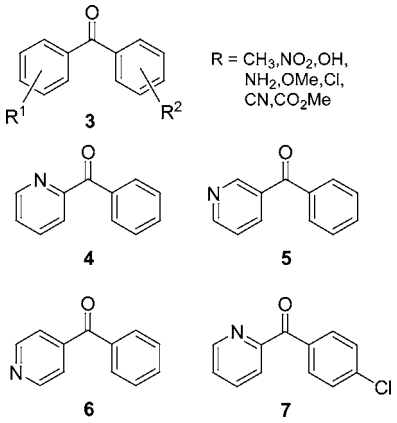

Figure 2. A range of substituted benzophenones and benzoylpyridine substrates

3n) substituted benzophenones. However, contrary to results obtained with most chemical catalyst reductions, ortho substitution was not required for good selectivity. Nitro substitution at the meta (**3d**) and para (**3e**) positions and *m*-chloro (**3m**) substitution provided for excellent selectivity (97−99% ee), while *p*-methyl (**3c**) substitution yielded 85% ee alcohol product. In comparison, the selective BINAP/chiral diamine Ru complex hydrogenation of *o*-methyl substituted **3a** was achieved with high enantioselectivity (>93% ee), but the hydrogenation of the *p*-methyl-substituted counterpart **3c** resulted in 8% ee alcohol product.[14]

Table 1. KRED-Catalyzed Reduction of Diaryl Ketones[a]

	ketone		(*R*)-alcohol		(*S*)-alcohol		yield of
no.	R^1	R^2	ee[b]	KRED[b]	ee[c]	KRED	**1g**,[d] %
3a	*o*-CH_3	−	**98**	121	**95**	119	95
3b	*m*-CH_3	−	72	121	−	−	
3c	*p*-CH_3	−	**85**	101	9	119	
3d	*m*-NO_2	−	34	111	>**99**	108	90
3e	*p*-NO_2	−	**96**	128	**97**	119	
3f	*o*-OH	−	**84**	111	−	−	
3g	*m*-OH	−	61	112	13	119	
3h	*p*-OH	−	69	113	55	117	
3i	*o*-NH_2	−	**91**	101	64	114	92
3j	*p*-NH_2	−	60	111	51	119	
3k	*p*-OMe	−	70	101	64	119	
3l	*o*-Cl	−	64	121	>**99**	118	
3m	*m*-Cl	−	39	111	>**99**	108	95
3n	*p*-Cl	−	64	101	−	−	
3o	*m*-CN	*p*-Cl	84	112	**90**	108	
3p	*m*-CO_2Me	*p*-Cl	33	115	>**99**	108	
4			**97**	101	77	119	
5			**82**	101	38	120	
6			44	*L.kefir*	>**99**	119	98
7			**94**	124	60	119	

[a] Reactions conditions: 30 °C, 2 g/L of KRED, 2 g/L of GDH, 20 g/L of glucose, 1 g/L of NADP, 10 g/L of ketone, 10% THF, in 100 mM potassium phosphate buffer (pH 7.0). [b] KRED number corresponds to the Biocatalytics catalog number. [c] Determined by chiral SFC analysis. Absolute configuration determined by comparison to literature data. [d] The 1 g reaction conditions (40 mL scale): 30 °C, 2 g/L of KRED, 2 g/L of GDH, 20 g/L of glucose, 1 g/L of NADP, 25 g/L of ketone, 10% THF, in 100 mM potassium phosphate buffer (pH 7.0). The product alcohol was extracted with 2× volumes methyl ethyl ketone. The organic phase was washed with 5 mL of DI water and dried. These reactions were run with the enzyme that produced the highest ee. The 1 g scale reactions were only run for those substrates that have a yield number listed.

Another trend observed for substrates with a single substitution on one of the phenyl rings was that electron-withdrawing groups generally provided for better selectivity than electron-donating groups. Nitro substitutions (**3d**, **3e**), for example, provided for much higher enantioselectivity than hydroxy- or methoxy-substituted diaryl ketones. The enzymatic reduction of *p*-nitro-substituted **3e** produced 97% ee alcohol product compared to 81.8% ee achieved with diphenylzinc aryl addition with a chiral pyrrolidinylmethanol catalyst.[22]

High selectivity was also observed in the substrates with substituents on both phenyl rings (**3o, 3p**). This result provides a significant advantage over the addition of aryl nucleophiles to aromatic aldehydes approach to the synthesis of diarylmethanols, since most aryl transfer reactions demonstrated thus far use diphenylzinc as the aryl source, and are therefore limited to phenyl transfers to aldehydes.[2] A further advantage is that the substrate need not be highly electronically dissymetric, as was required in the aforementioned CBS reduction of ketone **1**. The enzymatic reduction of ketone **3o** demonstrates that, even with electron-withdrawing substituents on both aryl rings, good selectivity (90% ee) can be obtained.

The benzoylpyridine derivatives (**4**, **5**, **6**, **7**) also exhibited highly selective reduction to their diarylmethanol counterparts with use of the KRED enzymes. Of particular interest is the alcohol produced from compound **7**, which is a precursor of the histamine H_1 antagonist (*S*)-carbinoxamine. The enantioselective enzymatic reduction of ketone **7** achieves excellent selectivity (94% ee). This intermediate is currently produced via the CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)-pyridinium triflate.[21] The allyl group is necessary to prevent the coordination of the pyridine nitrogen to the catecholborane or oxazaborolidine catalyst, and also serves to provide the steric bias necessary for a highly selective reduction. While the enzymatic reduction of **7** can be carried out with high selectivity, the CBS reduction of the unelaborated diaryl ketone **7** resulted in 11% ee at −78 °C (the low temperature was used to suppress the nonselective background reaction).[13]

In summary, a series of diaryl ketones consisting of mono- and disubstituted benzophenones and various benzoylpyridines has been successfully reduced to their respective diarylmethanols with moderate to excellent selectivity by using commercially available ketoreductase enzyme catalysts. Ortho substitution on one of the aryl rings was not a requirement for good enantioselectivity, nor was a highly electronically dissymmetric substrate. This work demonstrates the power of commercially available isolated enzymes to perform an important class of transformation (the reduction of diaryl ketones) that shows a significant advantage over

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standard chemical catalytic methods. These ketoreductase enzymes are shown to be extremely selective, and able to distinguish very subtle steric and electronic differences in diaryl ketone substrates, affording many diarylmethanol products with high ee.l

Supporting Information Available: General diaryl ketone reduction protocols as well as HPLC and SFC analysis methods (enantiomeric excess of the alcohol products was determined by SFC analysis and absolute configuration and identity of the alcohol products were determined by comparison to literature references). This material is available free of charge via the Internet at http://pubs.acs.org.

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