



Dynamic kinetic resolution of racemic α -sulfonylaldehydes via asymmetric transfer hydrogenation

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ABSTRACT

Hydrogen transfer reduction of α -sulfonylaldehydes using HCOOH–Et₃N system as hydrogen source and (S,S)-TsDPEN-based Ru(II) as catalyst proceeds with dynamic kinetic resolution, providing optically active β -sulfonyl primary alcohols in moderate-to-good yields and up to 90% ee.

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Asymmetric transfer hydrogenation, which recently emerged as a powerful alternative for the catalytic hydrogenation of polar C=O and C=N bonds,¹ has also been applied to the synthesis of compounds with two or more stereogenic centers from those substrates that have configurationally labile groups, via dynamic kinetic resolution (DKR).

Chiral Ru(*p*-cymene)TsDPEN is an excellent catalyst for the asymmetric transfer hydrogenation which is involved in the DKR-hydrogenation process of various ketones, providing the corresponding products with high de and ee values,² such as the reduction of 1-aryl-2-tetralones.³ It is also popular for the dynamic kinetic resolution of 1,3-dicarbonyl compounds in high ee,⁴ where Cossy and co-workers have extended the use of this methodology to the kinetic resolution of racemic 2-alkyl-1,3-diketones.⁵ Lassaletta and co-workers extended the scope of this methodology to a variety of cyclic α -haloketones, offering an efficient tool for the synthesis of chiral halohydrins in good-to-excellent yields and stereoselectivities, using either HCOOH/TEA or HCOOH/TBAB as the hydrogen source.⁶ Wagner and co-workers introduced perfluorosulfonyl groups into the chiral ligand designed for the DKR of β -oxo- α -amino acid, to improve the selectivity of the reaction.⁷ The first example of asymmetric transfer hydrogenation reduction of C=N bonds proceeding via DKR was reported by Lassaletta and co-workers.⁸ Similarly, they stereoselectively synthesized *syn* β -hydroxy cycloalkane carboxylates by using asymmetric transfer hydrogenation of cyclic β -keto esters via DKR.⁹ In the catalytic asymmetric hydrogenation/transfer hydrogenation of prochiral ketones, at least one new stereogenic center was generated.¹⁰ However, no new stereogenic center was generated in the hydrogenation/transfer hydrogenation of α -branched aldehydes, which makes the enantiocontrol of the reaction extremely difficult. Thus, the asymmetric hydrogenation/transfer hydrogenation of

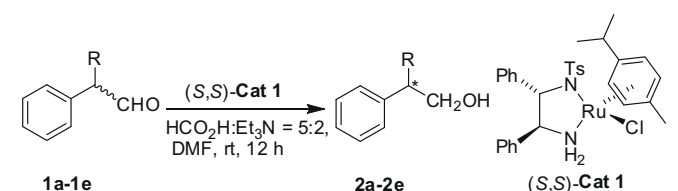
α -branched aldehydes still remains a challenge to chemists.¹¹ Very recently, List and Li reported the asymmetric hydrogenation of α -arylaldehydes catalyzed by [RuCl₂(xylyl-BINAP)(DPEN)], providing the corresponding primary alcohols in excellent enantioselectivities and yields.¹² A novel class of chiral spiro diphosphine (SDP) ligands has been developed by Zhou and co-workers.¹³ A SDP-based Ru catalyst, [RuCl₂(S)-DMM-SDP]((R,R)-DACH), was successfully applied to the enantioselective hydrogenation of α -arylaldehydes, providing an efficient synthesis of optically active primary alcohols.¹⁴

Optically active β -hydroxy sulfones are useful chiral synthons for the synthesis of biologically active molecules such as γ -butenolides,^{15a-c} γ -butyrolactones,^{15d} 2,5-substituted tetrahydrofuran, and δ -valerolactones.^{15e} As a result, many methods have been developed for the enantioselective synthesis of optically active β -hydroxy sulfones, including kinetic resolution,¹⁶ dynamic kinetic resolution,¹⁷ and/or kinetically controlled oxidation of racemic substrates by biocatalysts,¹⁸ baker's yeast or fungus¹⁹-mediated reduction, and chiral oxazaborolidine²⁰ or polymer-supported sulfonamide²¹-catalyzed borane reduction of β -keto sulfones. Genêt and co-workers reported an enantioselective hydrogenation of β -keto sulfones with chiral Ru(II) catalyst,²² and Hou and co-workers reported Rh-catalyzed enantioselective hydrogenation of β -keto sulfones using a bisferrocenyl diphosphine ligand with planar chirality.²³ However, reduction of aromatic analogues required drastic reaction conditions to obtain high optical purity or more expensive Rh catalyst should be employed. Zhang and co-workers reported Ru-based catalytic, highly enantioselective hydrogenation of β -keto sulfones using a new chiral biaryl phosphine ligand in the presence of iodine additives.²⁴

If one of two enantiomers of the racemic aldehyde can be selectively reduced by catalytic transfer hydrogenation and the remaining enantiomers can be rapidly racemized under the same conditions, then ultimately two enantiomers of the aldehyde will be fully converted to primary alcohols enantioselectively.

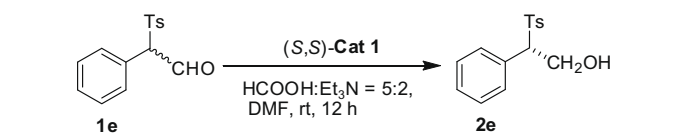
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Table 1
Asymmetric transfer hydrogenation of various α -branched aldehydes



Entry	R	Yield (%)	ee (%)
1	PhC=O (1a)	89	42
2	CN (1b)	—	—
3	CO ₂ Et (1c)	85	28
4	PO(OEt) ₂ (1d)	—	—
5	Tosyl (1e)	89	90

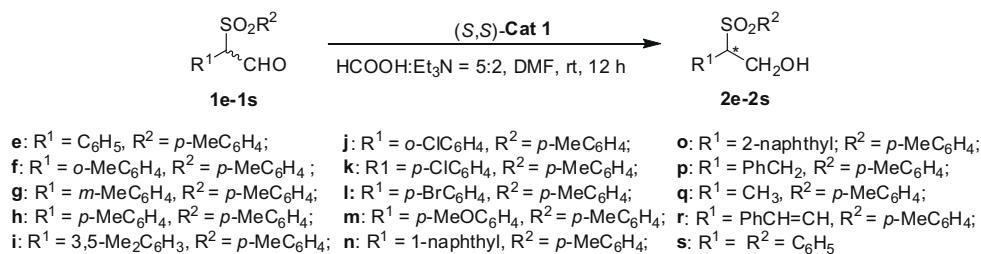
Table 2
Influence of the solvent and the substrate/catalyst ratio on the DKR of **1e**^a



Entry	Solvent	S/C	Yield (%)	ee (%)
1	DMF	80	89	90
2	DMSO	80	82	89
3	CH ₃ OH	80	85	88
4	THF	80	83	87
5	CH ₂ Cl ₂	80	—	—
6	Toluene	80	—	—
7	Solvent-free	80	80	86
8	DMF	40	92	86
9	DMF	120	89	87
10	DMF	160	88	88

^a The reaction was conducted under argon atmosphere.

Table 3
Transfer hydrogenation/DKR of various 2-sulfonyl aldehydes



Entry ^a	R ¹	R ²	Product	Yield ^b (%)	ee ^c (%)	[α] _D ^{24,d}	Config.
1	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄	2e	89	90	+72.5	S
2	<i>o</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2f	78	24	+12.2	
3	<i>m</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2g	83	83	+64.4	S
4	<i>p</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2h	86	88	+82.0	S
5	3,5-Me ₂ C ₆ H ₃	<i>p</i> -MeC ₆ H ₄	2i	84	86	+55.5	S
6	<i>o</i> -ClC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2j	73	34	-14.4	
7	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2k	88	89	+77.9	S
8	<i>p</i> -BrC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2l	92	88	+75.9	S
9	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	2m	90	84	+82.5	S
10	1-Naphthyl	<i>p</i> -MeC ₆ H ₄	2n	77	18	-12.0	
11	2-Naphthyl	<i>p</i> -MeC ₆ H ₄	2o	87	87	+91.2	S
12	Bn	<i>p</i> -MeC ₆ H ₄	2p	86	59	-5.9	
13	Me	<i>p</i> -MeC ₆ H ₄	2q	62	81	-4.7	
14	PhCH=CH	<i>p</i> -MeC ₆ H ₄	2r	80	81	+80.2	
15	C ₆ H ₅	C ₆ H ₅	2s	81	89	+72.3	S

^a All the substrates were synthesized from the corresponding aromatic halides.

^b Isolated yield after column purification.

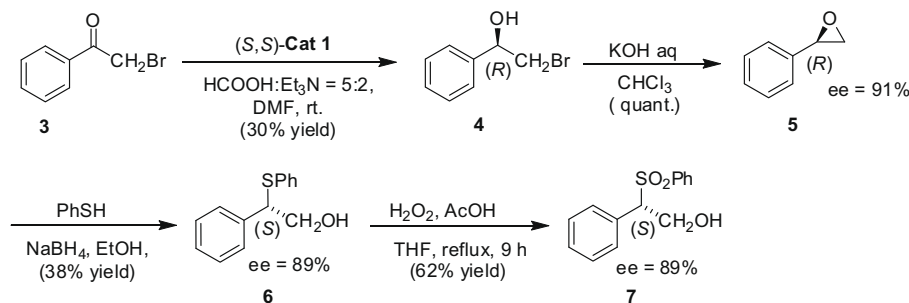
^c Ee values were determined by HPLC on a Chiralpak AD-H/or Chiralcel OD-H column.

^d Measured in acetone at 289 nm.

This process is termed as the asymmetric transfer hydrogenation of racemic aldehyde via DKR. Hydrogen-transfer reduction of α -branched aldehydes has been reported,¹¹ but asymmetric version of this reaction has not been documented. In studying the synthesis of biologically active compounds, we became interested in developing methods for the asymmetric synthesis of chiral primary alcohols. We chose several α -branched aldehydes as the substrates for the synthesis of the corresponding optically active primary alcohols by using asymmetric transfer hydrogenation reaction with HCOOH/TEA as the hydrogen source and (S,S)-Cat 1 as the catalyst (Table 1). It was found that the asymmetric transfer hydrogenation of **1e** (R = Tosyl) resulted in the efficient DKR of the substrate, and provided a practical access to chiral primary alcohols in excellent enantiomeric excess (up to 90% ee) and in high yield (up to 89% yield) (entry 5). So far, synthesis of optically active β -sulfonyl primary alcohols by using asymmetric transfer hydrogenation of α -sulfonylaldehydes via DKR has not been reported.

Using the asymmetric hydrogen transfer reaction of **1e** (R = Tosyl) as a model reaction, the solvent, substrate/catalyst ratio were examined with Cat 1 in order to improve the enantioselectivity (Table 2). In solvents of low polarity such as CH₂Cl₂ and toluene, no product could be detected by TLC (entries 5 and 6). In contrast, polar solvents such as DMF, DMSO, CH₃OH, and THF gave much better results (entries 1–4). However, none of them was found to be obviously superior than others. The enantioselectivity of the reaction under solvent-free conditions slightly decreased (entry 7). There was no major change in enantioselectivity, when the S/C ratio changed from 40 to 160 (entries 8–10).

With the optimized reaction conditions in hand, the scope of the reaction of the α -sulfonylaldehydes was investigated and the results are summarized in Table 3. Various α -sulfonylaldehydes (**1e–s**) were reacted in the presence of chiral catalyst (S,S)-Cat 1 (S/C = 80) using the HCOOH/Et₃N = 5:2 as hydrogen source in DMF at ambient temperature for 12 h. It was found that for all *meta*- or *para*-(un)substituted 2-phenyl-2-sulfonylacetalddehydes,



Scheme 1.

including 2-naphthylacetaldehyde, the reactions gave good yields (83–92%) and high selectivities (83–90% ee, entries 1, 3, 4, 5, 7, 8, 9, and 11). The reaction seems to be insensitive to the electronic nature of the substituents. However, the steric feature of the substrates plays an important role. Thus, *ortho*-substitution including electron-donating and electron-withdrawing substitution, resulted in lower yield and dramatically decreased enantioselectivity (entries 2, 6, and 10). 3-Substituted 2-sulfonylpropanals also underwent this reaction smoothly (entries 13–15).

The absolute configuration of the product **2s** was determined according to the procedure shown in Scheme 1. Enantioselective transfer hydrogenation of 2-bromo-1-phenylethanone **3** by using [RuCl₂(*p*-cymene)](S,S)-TsDPEN as the catalyst provided (*R*)-2-bromo-1-phenylethanol **4** according to the known procedure,²⁵ which was then converted into the (*R*)-2-phenyloxirane **5** by treatment with aqueous KOH.²⁶ Easy ring-opening of this compound with PhSH as the nucleophile²⁷ resulted in the formation of the (*S*)-2-phenyl-2-(phenylthio)ethanol **6**, which was then oxidized with H₂O₂–AcOH system to give the corresponding sulfone (*S*)-**7** without racemization.²⁸ The retention time of this compound was found equal to that of **2s**. Based on this, together with the fact that they have the same sign of optical rotation, the absolute configuration of **2s** should be (*S*). The configuration of compounds **2e**, **2g**, **2h**, **2i**, **2k**, **2l**, **2m**, and **2o** was assigned to (*S*) by analogy.

In conclusion, we have demonstrated that using [RuCl₂(*p*-cymene)](S,S)-TsDPEN as the catalyst, and HCOOH/Et₃N as the hydrogen source, a variety of 2-sulfonyl aldehydes could be reduced to the corresponding optically active primary alcohols with DKR in good yields and with up to 90% ee, providing an efficient method for the asymmetric synthesis of 2-sulfonyl primary alcohols.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.031.

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