Dynamic kinetic resolution of β-keto sulfones *via* asymmetric transfer hydrogenation†

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The dynamic kinetic resolution of β-keto sulfones was achieved *via* asymmetric transfer hydrogenation using (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) in the presence of formic acid and triethylamine afforded the desired products in good yield with up to >99 : 1 dr and high ee up to >99%.

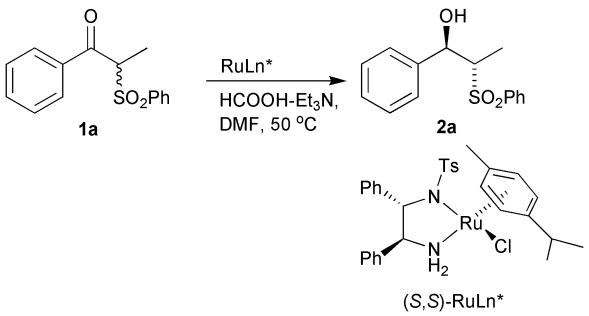
Dynamic kinetic resolution (DKR) is an efficient method to obtain optically pure compounds from racemic substrates, which combines the resolution step of kinetic resolution with an *in situ* equilibration or racemisation of the configurationally labile substrate.[1] Recently, increasing attention has been given to the discovery of DKR reactions, which can, theoretically, result in quantitative yield with enantiomeric excess (*ee*) approaching 100%.[2]

Hydrogen transfer reactions are mild methodologies for reduction of ketones or imines and oxidation of alcohols or amines in which a substrate-selective catalyst transfers hydrogen between the substrate and hydrogen donor or acceptor, respectively.[3] In recent years, hydrogen transfer reduction has gained a prominent position as to be rated second in order of importance immediately behind asymmetric hydrogenation with molecular hydrogen.[4]

To our knowledge, a few examples about DKRs have been reported *via* asymmetric transfer hydrogenation. Excellent examples include Noyori's reduction of benzils,[5] Cossy's reduction of 1,3-diketones[6] and reduction of cyclic β-keto esters, cycloalkylamines, β-keto-α-amino esters and cyclic ketones.[7]

Optically active β-hydroxy aryl sulfones are useful chiral synthons in organic synthesis.[8] Many methods have been developed for the enantioselective synthesis of optically active β-hydroxy sulfones, such as kinetic and dynamic kinetic resolution of racemic β-hydroxy sulfones[9] and asymmetric reduction of β-keto sulfones.[10] As these compounds are very useful, we designed the DKR of β-keto sulfones *via* asymmetric hydrogen transfer reaction to obtain enantiomerically enriched β-hydroxy sulfones.

We first chose the reduction of 1-phenyl-2-(phenylsulfonyl)-propan-1-one **1a** as our research model (Scheme 1).



Scheme 1 Dynamic kinetic resolution of 1-phenyl-2-(phenylsulfonyl)-propan-1-one **1a**.

While the reaction conducted at room temperature in DMF using (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylenediamine](*p*-cymene) (0.6%) as the catalyst and formic acid (5 equiv.)–triethylamine (2 equiv.) as the hydrogen source, the reaction was very slow and no product could be detected by TLC after 24 h. Considerable rate acceleration was observed by performing the reaction at 50 °C compared to room temperature, it gave a combined yield of 95% with 93 : 7 diastereomeric ratio (*dr*). The enantiomeric excess (*ee*) of the major and the minor diastereomers, determined by HPLC analysis, was 98 and 85%, respectively. The influence of reaction solvent on the DKR was then investigated. The results are shown in Table 1.

Table 1 **1** Solvent effects on the DKR of **1a**

Entry	Solvent	*t*/h	Yield[a] (%)	*dr*[b]	*ee*[b](%) major
1	DMF	12	95	93 : 7	98
2	THF	20	85	90 : 10	93
3	Toluene	20	88	90 : 10	92
4	Diisopropyl ether	12	80	86 : 14	97
5	DMSO	12	92	89 : 11	98
6	CH_3CN	12	85	89 : 11	98
7	CH_3OH	12	82	89 : 11	98

[a] Isolated yield. [b] Determined by chiral HPLC analysis using a Chiralpak AD–H column.

Table 2 Influence of the catalyst/substrate ratio on the DKR of **1a**

Entry	S/C	*t*/h	Yield[a] (%)	*dr*[b]	*ee*[b](%) major
1	40	12	92	88 : 12	97
2	80	12	95	93 : 7	98
3	120	24	85	89 : 11	98
4	160	24	70	90 : 10	99

[a] Isolated yields. [b] Determined by chiral HPLC analysis using a Chiralpak AD–H column.

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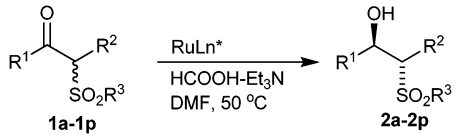
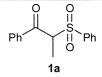
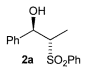
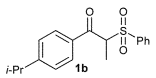
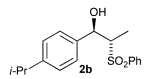
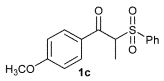
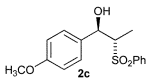
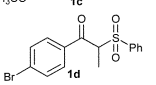
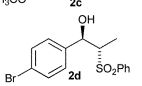
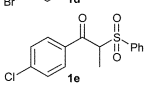
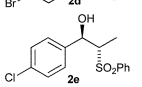
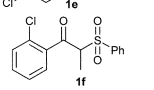
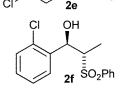
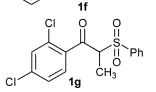
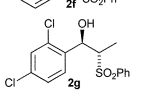
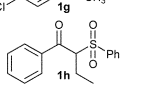
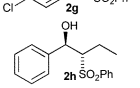
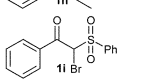
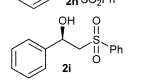
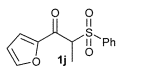
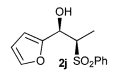
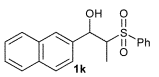
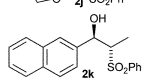
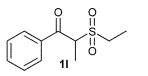
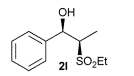
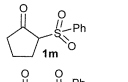
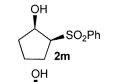
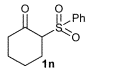
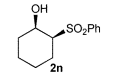
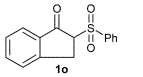
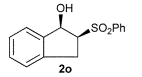
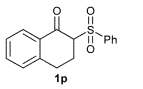
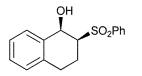
† Electronic supplementary information (ESI) available: General experimental procedure for the transfer hydrogenative DKR of the β-ketosulfones, ^1H and ^{13}C NMR spectra, HRMS spectra and HPLC data. CCDC 696276. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b818257d

Table 3 Results of DKR of **1a–1p** at 50 °C in DMF



Entry	Substrate	Product	Yield[a] (%)	*dr*[b]	*ee*[b] (%) major
1			95	93:7	98
2			85	86:14	99
3			<5	95:5	99
4			96	90:10	97
5			95	98:2	90
6			88	51:49	57
7			89	67:33	83
8			<5	nd	nd
9			96[c]	–	99
10			89	95:5	>99
11			95	87:13	98
12			94	90:10	>99
13			90	99:1	84
14			87	98:2	65
15			90	>99:1	>99
16			92	>99:1	>99

[a] Isolated yield. [b] Determined by chiral HPLC analysis using a Chiralpak AD–H column or Chiralcel OD–H column. [c] The product was 1-phenyl-2-(phenylsulfonyl)ethanol.

The data demonstrate that excellent results could be obtained in many solvents explored, such as DMF, CH_3OH, CH_3CN and DMSO. In THF and in toluene, the reaction was slower. When DMF was employed as the solvent, it gave the highest yield, diastereomer ratio and *ee* for the major isomer. So we chose DMF as the solvent to investigate the influence of the catalyst/substrate ratio on the DKR of **1a**. The results are listed in Table 2.

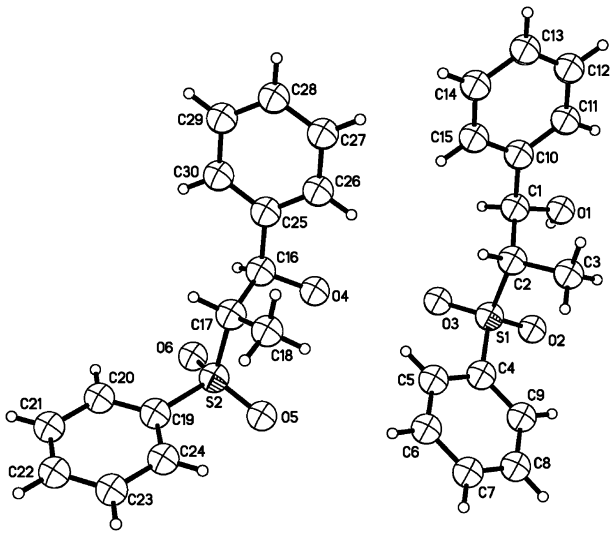


Fig. 1 X-Ray crystal structure of the major diastereomer of **2a**.

The diastereo- and enantioselectivity of the transformation was only marginally influenced by the catalyst/substrate ratio. However, longer reaction time was necessary at lower catalyst loading.

DKR reactions of many other β-keto sulfones[11] were then investigated at 50 °C using DMF as the solvent.[12] The results are summarized in Table 3.

Data showed that substitution in benzene ring did significantly affect the reaction, the substrates with electron-withdrawing group such as *p*-chloro gave faster reaction, while the electron-donating such as *p*-methoxy group deactivated the reaction (entries 1–5). With the *o*-chloro substrates, the *dr* and *ee* dropped sharply (entries 6 and 7). The reduction of cyclic β-keto sulfones gave excellent *dr*.

For the absolute configuration assignment, single crystals of the major diastereomer of **2a**, were prepared and the structure established by X-ray crystallography. According to the results of the major diastereomer of **2a**,[13] there are two independent molecules in the asymmetric unit. They have the same absolute configurations of (1*R*,2*S*) (Fig. 1).

In summary, a convenient and highly stereoselective approach to chiral β-hydroxy sulfones has been developed. The asymmetric transfer hydrogenation of the corresponding sulfones by using Noyori's Ru(cymene)-TsDPEN catalyst and HCOOH–Et_3N as the hydrogen source proceeds *via* dynamic kinetic resolution to selectively afford (1*R*,2*S*)-compounds for a variety of substrates. Remarkable results concerning the reactivity and enantioselectivities (>99 : 1 dr, >99% ee) were achieved for rigid cyclic α-tetralone and α-indanone derivatives.

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12 Dynamic kinetic resolutions (DKR) of 1-phenyl-2-(phenylsulfonyl)-propan-1-one (**1a**)—A general procedure: A suspension of $[RuCl_2(p\text{-cymene})]_2$ (3.75 mg, 0.00625 mmol) and (*S*,*S*)-TsDPEN (4.58 mg, 0.0125 mmol) in DMF (0.5 mL) was degassed three times, and then stirred at 80 °C for 1 h. After cooling to room temperature, 5 : 2 HCOOH–Et_3N (0.2 mL) was added, and then **1a** (0.5 mmol) was added. The reaction was stirred at 50 °C until completion according to TLC detection. 5.0 mL water was added to the reaction, the mixture was then extracted three times with EtOAc (10 mL), dried over anhydrous sodium sulfate and concentrated. After removal of the solvent, the residue was purified by flash column chromatography (silica gel H, EtOAc–petroleum = 1 : 2) to give the pure product, 95% yield, which was determined by HRMS, IR, ^{1}H and ^{13}C NMR spectroscopy. 1-phenyl-2-(phenylsulfonyl)propan-1-ol (**2a**): white solid; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, J = 7.1 Hz, 3H, CHC*H*$_3$), 3.21–3.26 (q, J = 7.2 Hz, 1H, CHC*H*CH$_3$), 3.28 (s, 1H, O*H*), 5.54 (s, 1H, C*H*OH), 7.26–7.36, (m, 5H, Ar–*H*), 7.65 (t, J = 7.3 Hz, 2H, Ar–*H*), 7.74 (t, J = 7.5 Hz, 1H, Ar–*H*), 7.99 (d, J = 8.3 Hz, 2H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 6.21, 66.09, 69.68, 125.98, 128.20, 128.90, 129.17, 129.86, 134.57, 137.75, 140.24; IR (film) ν_{max}/cm^{-1} 3480.1, 1591.5, 1448.5, 1295.1, 1189.0, 1143.8, 1080.9, 761.6, 725.7, 697.3; HRMS (EI): m/z = 276.0820 (calc. for $C_{15}H_{16}O_3S$ = 276.0820); HPLC: Chiralpak AD-H (*i*-PrOH–hexane, 10 : 90, flow rate 1 mL min^{-1}, λ = 210.5 nm): t_1 = 13.814 min, t_2 = 18.318 min, t_3 = 22.008 min, t_4 = 23.733 min; $[\alpha]_D^{24}$ = −12.86 (c = 1.0, acetone), dr = 97 : 3, ee = 98%.

13 Careful evaporation of a solution of **2a** in AcOEt–petroleum (1 : 4) gave single crystals which were suitable for crystallographic analysis. Selected crystal structure data: $C_{15}H_{16}O_3S$, space group $P2_1$, a = 10.4899(19), b = 11.433(2), c = 11.813(2) Å, β = 100.702(4)°, V = 1392.0(4) Å^3, Z = 2, T = 293 K, R (reflections) = 0.0510, w$R2$ (reflections) = 0.1081.