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COMMUNICATION

Highly Enantioselective Transfer Hydrogenation of Racemic α-Substituted β-keto Sulfonamides *via* Dynamic Kinetic Resolution

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Highly enantioselective transfer hydrogenation of β-keto sulfonamides was developed *via* dynamic kinetic resolution using a chiral Ru(II) catalyst with an azeotropic solution of HCO_2H/Et_3N as a hydrogen donor, affording α-substituted β-hydroxyl sulfonamides in good yields with excellent diastereo- and enantio-selectivities. This method is featured with mild conditions, easy operation, and a broad substrate scope which makes it possible to find wide applications in synthesis of nature products and biologically active compounds containing α-substituted β-hydroxyl sulfonamides core.

Sulfa drugs, important synthetic antimicrobial agents containing sulfonamide group, have been widely used in clinical treatment for more than 80 years.[1] Thus, sulphonamides are regarded as privileged motifs for lead compounds in drug discovery and attracted great attention.[2] Great efforts have been devoted to the development of efficient methods for constructing of functionalized sulfonamides and many approaches have been developed.[3] However, the asymmetric access to α-substituted β-hydroxyl chiral sulfonamides is still rare[4] despite these compounds are widely distributed in dugs and nature products and exhibit important biological activities (Figure 1),[5] thus the development of efficient methods for α-substituted β-hydroxyl chiral sulfonamides is highly desirable.

In the past decades, dynamic kinetic resolution (DKR) as an efficient methodology to obtain optically pure molecules from racemic compounds has been widely investigated.[6-7] Among them, asymmetric hydrogenation of racemic α-substituted ketones *via* dynamic kinetic resolution (DKR) has been demonstrated to be an efficient and reliable method for the synthesis of chiral α-substituted β-hydroxyl compounds with two contiguous stereocenters. However, most of these reactions were conducted under basic condition, making base-sensitive substrates, such as α-halo ketones, unfit for this transformation, which greatly limited the substrate scope.[8] Compared with traditional hydrogenation, asymmetric transfer hydrogenation(ATH)[9] has better compatibility to substrates and is more suitable for the reduction of sensitive or complicated substrates, such as α-halo ketone.[10] Even so, when racemic α-halo ketone was used in ATH *via* dynamic kinetic resolution, the dehalogenation product was obtained. For example, α-alkyl β-keto sulfones were well tolerated in ATH via dynamic kinetic resolution, but α-bromo β-keto sulfone only afforded debromination product in the same conditions.[11] Therefore, to develop a general and efficient method for hydrogenation of α-substituted β-keto sulfones/sulphonamide with excellent compatibility to substrate is still a challenge. Herein, we disclose the highly enantioselective transfer hydrogenation of racemic α-substituted β-keto sulfonamides with ruthenium catalyst for the synthesis of α-substituted β-hydroxyl sulfonamides. More

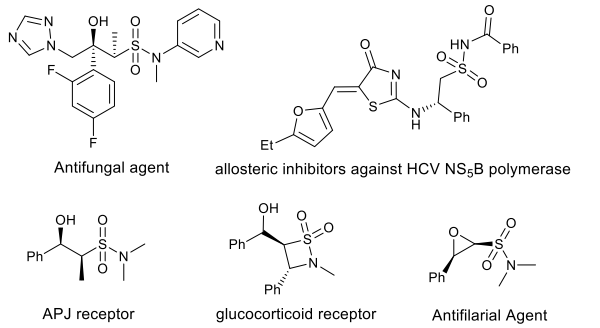

Figure 1 Biologically active compounds containing chiral β-hydroxyl sulfonamides.

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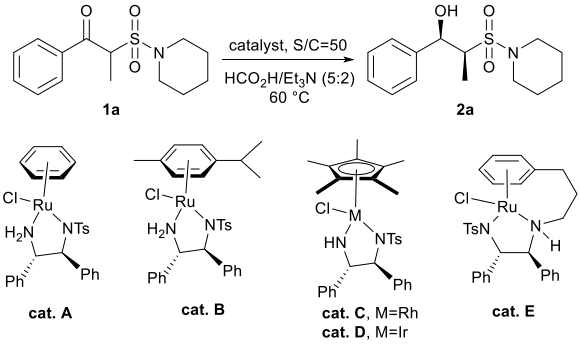
‡ Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of compounds. See DOI: 10.1039/x0xx00000x

importantly, α-halo substituted β-keto sulfonamides, challenging substrates for hydrogenation, are also well-tolerated in this reaction.

The asymmetric transfer hydrogenation of racemic 1-phenyl-2-(piperidin-1-ylsulfonyl) propan-1-one (**1a**) was chosen as model reaction to optimize the reaction conditions. Initially, a variety of catalysts were examined. As showned in Table1, when half-sandwiched Ru(II)/η^6-arene catalysts were used (entries 1-2), they both showed acceptable results, but **cat. B** did better in yield, enantio- and diastereoselectivity. This was probably due to the methyl and 2-propyl group on the arene ring and thus increased the reactivity and steric hindrance. When Rh (III) or Ir (III) complex was employed in this reaction, only moderated yields and enantioselectivities were obtained (entry 3-4). This might suggest that ruthenium (II) is more suitable for the transfer hydrogenation of **1a**. Therefore, Ru-tethered **cat. E** developed by Wills group[12] was investigated, the reaction proceeded very smoothly, affording the desired product in high yield with excellent enatio- and diastereoselectivity (entry 5). Subsequently, alternative molar ratios of HCO_2H/Et_3N were tested, and the results revealed that a molar ratio of 5:2 is the best condition in comparison to that of 3:2 or 1:1(entries 6-7).

Table 1 Influence of the catalyst on the ATH-DKR of **1a**

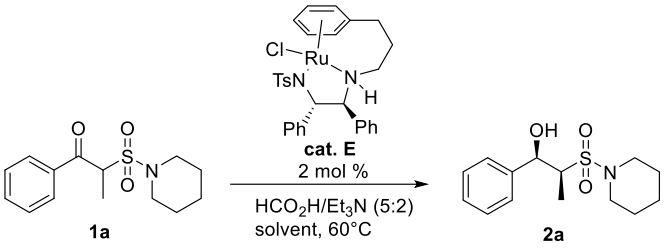


Entry[a]	catalyst	yield[b]%	ee[c]%	dr[d]
1	**cat. A**	80	90	2:1
2	**cat. B**	90	96	9:1
3	**cat. C**	62	41	6:1
4	**cat. D**	58	32	5:1
5	**cat. E**	98	98	12:1
6[e]	**cat. E**	98	95	10:1
7[f]	**cat. E**	98	94	12:1

[a] All reactions were carried out by using **1a** (0.08mmol), catalyst (0.0016mmol), 5:2 HCO_2H/Et_3N (1 mL) under argon protection at 60 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis using a Chiralpak AD-H column. [d] Determined by NMR. [e] 3:2 HCO_2H/Et_3N was used. [f] 1:1 HCO_2H/Et_3N was used.

Inspired by these promising results, we investigated the solvent effects in the presence of 2 mol% **cat. B** by using formic acid/triethylamine (molar ratio 5:2) as hydrogen source. As shown in Table 2, the solvents tested here have no influence to the enantioselectivity and all of them afford desired product with excellent enantioselectivity, but it have an important impact on the yield. When the reaction was conducted in EtOH, dioxane, toluene, only moderated yields were obtained. When MeOH, THF, CH_3CN, DMF were employed as solvents, this reaction proceeded very smoothly, affording target product in excellent yields with high diastereo- and enantioselectivities. It's worth noting that this reaction also proceeded very well in the mixture of HCO_2H/Et_3N. Due to the relatively high diastereoselectivity, DMF was chosen as the best solvent. Subsequently, the reaction temperature was evaluated, and the results disclosed that decreasing temperature lead to a relatively low yield (entries 9-10).

Table 2 Influence of the solvents on the ATH-DKR of **1a**



Entry	solvent	yield (%)[b]	Ee(%)[c]	dr[d]
1	MeOH	>99	>99	12:1
2	EtOH	50	>99	12:1
3	THF	>99	>99	12:1
4	Dioxane	36	>99	15:1
5	CH_3CN	>99	>99	15:1
6	Toluene	45	>99	15:1
7	DMF	>99	>99	>20:1
8[e]	-	>99	>99	15:1
9[f]	DMF	90	99	20:1
10[g]	DMF	95	98	20:1

[a] Unless otherwise noted, all reactions were carried out with a substrate/catalyst ratio of 50:1 at 60 °C for 12 h. [b] Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Determined by ^{1}H NMR spectroscopy. [e] 1 mL HCO_2H/Et_3N mixture was used. [f] room temperature, 24h. [g] 40 °C, 18h.

Under the optimal reaction conditions, the substrate scope was investigated. As shown in Table 3, the electronic properties and the position of substituent group on benzene ring has no influence on the reaction, all α-substituted β-aryl keto sulfonamides examined here can be hydrogenated efficiently, giving desired products with good yield, high enantioselectivity and excellent diastereoselectivity (**2a**-**2g**). Replacing aryl group by polycyclic aromatic group or heteroaromatic group, such as naphthyl and thienyl, this reaction also proceeded very well (**2h**-**2i**). When piperdinyl group of sulfonamide was changed to pyrrolyl group, morpholinyl group or dimethyl group (**2j**-**2l**), there are no influence to this reaction. In addition, α-methyl β-

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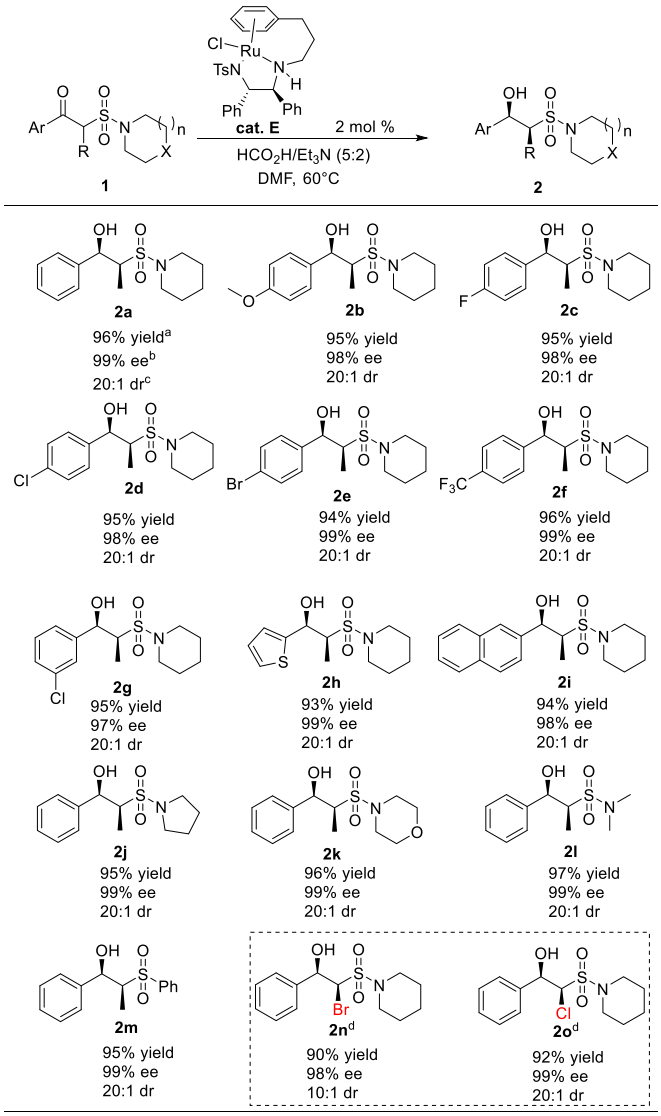
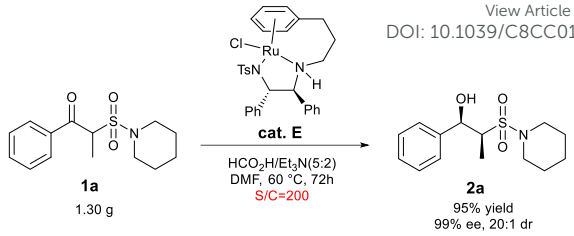
keto sulfone was also worked very well in this reaction (**2m**).[13] It is worthy to note that this reaction exhibited a good tolerance to various α-functional group substituted β-keto sulfonamides. When the substituent R changed to a sensitive halogen group, it also gave target products with excellent results (**2n**-**2o**). To the best of our knowledge, this work represents the first example to construct α-halo β-hydroxy compounds with two contiguous chiral centers by reduction of α-halo ketones *via* dynamic kinetic resolution.

Table 3 ATH-DKR results of **1a**-**1o**[a]



[a] All reactions were carried out with a substrate/catalyst ratio of 50:1 at 60 °C for 12 h. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. dDetermined by ^{1}H NMR spectroscopy. [d]The reaction was conducted at room temperature for 18 h.

In order to demonstrate the potential practical application of this reaction, a gram scale reaction was performed at 60°C in presence of 0.5 mol% catalyst loading. As shown in Scheme 1, the reaction proceeded smoothly, affording **2a** in 95% yield with 99% enantioselectivity and 20:1 diastereoselectivity.



Scheme 1 Gram scale reaction.

In summary, we have developed an efficient and practical strategy for the synthesis of α-substituted β-hydroxyl sulfonamides by a tethered Ru (II) complex catalyzed transfer hydrogenation of racemic α-Substituted β-keto sulfonamides. The reaction features wide substrate scope, high yield, excellent diastereo- and enantioselectivity, which make it possible to find wide applications in the synthesis of biologically active compounds containing β-hydorxy sulfonamides core. Further investigation on asymmetric hydrogenation of α-functionalized ketones is also underway in our laboratory.

We are grateful for financial support from the National Natural Science Foundation of China (Grant Nos. 21402145, 21432007, and 21372179), the Youth Chen-Guang Science and Technology Project of Wuhan City (2015071704011640), the Natural Science Foundation of Hubei Province (2014CFB181), the Fundamental Research Funds for Central Universities (2042017kf0177), the Important Sci-Tech Innovative Project of Hubei Province (2015ACA058), Open found of CAS Key Laboratory of Molecular Recognition and Function (2017LMRF002) and the "111" Project of the Ministry of Education of China.

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13 The absolute configuration of **2m** was confirmed to be (1*R*, 2*S*) by comparison specific optical rotation with Ref 11. All the other configurations are uncertain and based on the assumption that the configuration follows that of **2m**.

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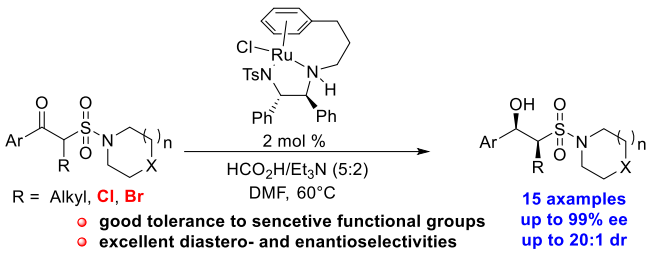

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