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Selective Asymmetric Transfer Hydrogenation of α-Substituted Acetophenones with Bifunctional Oxo-Tethered Ruthenium(II) Catalysts

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Abstract. A practical method for the asymmetric transfer hydrogenation of α-substituted ketones was developed utilizing oxo-tethered *N*-sulfonyldiamine-ruthenium complexes. Reduction by HCO_2H and HCO_2K in a mixed solvent of EtOAc/H_2O allowed for the selective synthesis of halohydrins from 2-bromoacetophenone (98%) and 2-chloroacetophenone (>99%), leading to suppressed undesired side reactions stemming from formylation under the typical reaction conditions using an azeotropic 5:2 mixture of HCO_2H and Et_3N. A range of functional groups, such as halogens, methoxy, nitro, dimethylamino, and ester groups, were well tolerated, highlighting the potential of this method. Nearly complete selectivity with a preferable ee was maintained even with a substrate/catalyst (S/C) ratio of 5000. This catalyst system was also effective for the asymmetric reduction of α-sulfonated ketones without eroding the leaving group.

Keywords: asymmetric catalysis; asymmetric transfer hydrogenation; ruthenium; α-haloketones; halohydrins

Asymmetric transfer hydrogenation (ATH) of prochiral ketones is one of the most extensively researched areas in the synthesis of chiral secondary alcohols.[1] Compared with asymmetric hydrogenation, ATH without hazardous hydrogen gas ensures several advantages, such as mild reaction conditions and a simple and safe operation. Based on the crucial role of protic amine ligands in the asymmetric reduction of polar carbon-oxygen and carbon-nitrogen double bonds, Noyori's well-defined chiral Ru(II) catalysts, such as RuCl(TsDPEN)(*p*-cymene) (**1**; TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine), have proven to be applicable to ATH of various prochiral ketones. ATH has become a viable option in the industrial production of chemical compounds, particularly active pharmaceutical ingredients (APIs).[2] In the context of our ongoing interest in accessing synthetically valuable chiral alcohols, the ATH of α-bromoacetophenone is a remaining challenge. Optically pure 2-bromo-1-arylethanols and the related 2-amino-1-arylethanols are key intermediates of pharmaceuticals, such as β-adrenergic receptor agonists;[2d,3] however, it has been reported that α-bromoketones decompose under ATH conditions using a mixture of HCO_2H/Et_3N.[2d,4a] The Corey-Bakshi-Shibata (CBS) reduction[3c,3e-f,5] and a biocatalytic reaction[6] have been alternatively executed for this purpose. In reasonable efforts to utilize formic acid and its analogues as convenient reducing agents for the enantioselective reduction of α-bromoketone,[3e,4] specially modified water-soluble ligands or surfactants were treated in an aqueous-phase ATH reaction to dissolve hydrophobic metal complexes in the reaction media. Although some rhodium and iridium catalysts have provided more satisfactory results than the ruthenium system, a comparatively substantial amount of expensive catalyst was used (typically with a substrate/catalyst ratio (S/C) of 100).[4d,e,j] A one-pot sequential process involving a Au-catalyzed hydration of aryl-substituted bromoalkynes and the ATH of the resulting bromomethyl ketones, which was recently examined as a practical approach for the construction of chiral aromatic bromohydrins, was conducted using 1.5 mol% each of $IPrAuNTf_2$ and RuCl(TsDPEN)(η^6-mesitylene).[4i]

In our previous studies, advanced oxo-tethered ruthenium complexes (*S*,*S*)-**2** and (*S*,*S*)-**3**[7,8] showed much higher activity in the ATH of acetophenone (with up to S/C = 30,000) than the prototypical ATH catalyst **1** (Figure 1).[1a-e,7a] Herein, we report a new application of the oxo-tethered complexes for the

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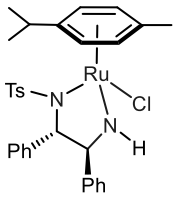
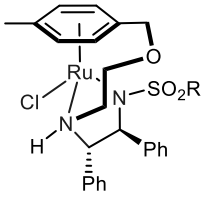
reduction of α-bromoketone and related substituted acetophenones having good leaving groups, leading to exceptionally high product selectivity.

Figure 1. Structure of non-tethered and tethered Ru-DPEN catalysts.



(*R*,*R*)-**1** RuCl(Tsdpen)(*p*-cymene)

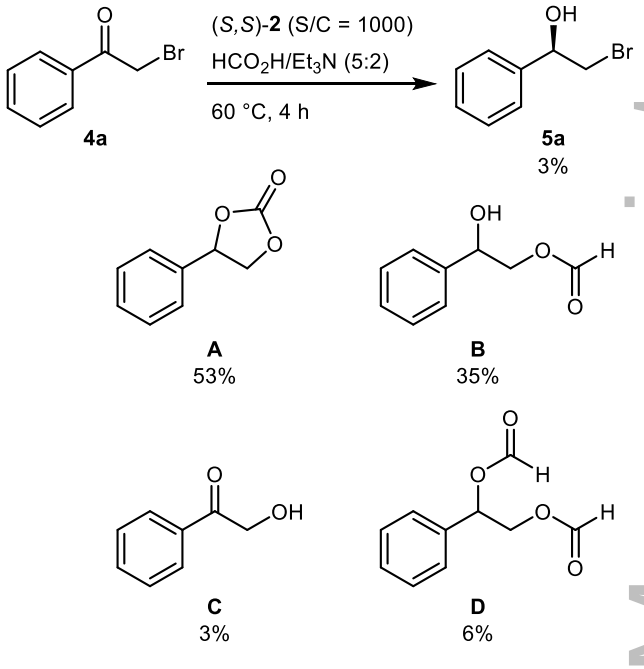


SO_2R= Ts (*S*,*S*)-**2** TsDENEB
Ms (*S*,*S*)-**3** MsDENEB

Our initial study started with the ATH of 2-bromoacetophenone (**4a**) as a model substrate at 60 °C for 4 h. The results are summarized in Table 1. When (*R*,*R*)-**1** was used as a catalyst in a 5:2 mixture of HCO_2H and Et_3N (run 1), **4a** was mostly consumed as expected, and only a trace amount of bromohydrin (**5a**) was detected by GC analysis. Upon changing the catalyst to the oxo-tethered complex (*S*,*S*)-**2**, the yield of **5a** slightly increased to 4% (run 2). Although no marked effect was observed using EtOAc as a solvent (run 3), the addition of water was found to give (*R*)-**5a** with 40% selectivity and 96% ee (run 4). Gratifyingly, a combined use of HCO_2H and HCO_2K, instead of a HCO_2H/Et_3N azeotrope, drastically enhanced the selectivity up to 98% (run 5). Among the tested solvents (runs 5-10), BuOAc and toluene also showed acceptable selectivities, albeit with somewhat lower catalytic activities (runs 6 and 7). The use of methanol and THF gave rise to rather poor product selectivities (runs 8 and 9). Although a more favorable result with an excellent yield and 97% ee was obtained for $CHCl_3$ (run 10), we preferred to use EtOAc as a desirable solvent from both an environmental and practical point of view. When the reaction was conducted without HCO_2K, the catalytic activity, selectivity, and optical purity dropped noticeably (run 11). It should be noted that the conversion and selectivity to (*R*)-**5a** dramatically reverted in the presence of only 0.1 equiv. of HCO_2K (run 12), and the further addition of an excess amount of HCO_2K led to an increase in the enantioselectivity and a slight decrease in the chemoselectivity (run 13). A considerable decrease in the product selectivity using HCO_2K as the sole hydrogen source signified that HCO_2H and HCO_2K were both indispensable for the exquisite catalytic performance (run 14). Eventually, it turned out that the combined use of 3.0 equiv. of HCO_2H and 1.0 equiv. of HCO_2K was optimal for this reaction.

Further study on the ATH of **4a** with (*S*,*S*)-**2** in a HCO_2H/Et_3N azeotrope (run 2 of Table 1) by GC and LC-MS analyses revealed that cyclic carbonate (**A**) and a formate derivative (**B**) were produced in 53% and 35% yields, respectively, accompanied with small amounts of α-hydroxyketone (**C**) and glycol diformate (**D**) as shown in Scheme 1. Debrominated acetophenone or 1-phenylethanol was not confirmed in the product mixture. The formation of **A** and **B** is in accordance with previously reported results[2d,4a].

Scheme 1. Formation of byproducts in the typical ATH system using HCO_2H/Et_3N.



According to the relevant carbonate formation mechanism in the ATH of α-sulfonated acetophenone by the Wills' group, the formation of **A** by debromination of **4a** is conceivable, as shown in Scheme 2.[9] With the progress of the ATH of **4a**, the alcoholic group of **5a** can trap CO_2 in the presence of Et_3N, followed by concomitant cyclization and debromination to afford **A**. Considering the formate anion in the azeotrope, debromination leading to **B** is ascribed to the nucleophilic substitution of **4a** or **5a** by HCO_2^-. Based on these mechanistic aspects, high selectivity of the present HCO_2H/HCO_2K ATH system was realized by eliminating Et_3N, which is intimately involved in the formation of the debromination products **A** and **B**. Actually, formate **B** was obtained as a sole product in 32% yield, when bromohydrin **5a** was treated under the ATH conditions using HCO_2H/Et_3N. Carbonate **A** was not formed in this experiment because of the absence of CO_2. When **5a** was subject to the ATH conditions under CO_2 atmosphere, formation of carbonate **A** from bromohydrin was verified by GC/MS analysis. In contrast, the Et_3N-free HCO_2H/HCO_2K system in a mixture of EtOAc and H_2O could suppress such excessive side reactions via **5a**.

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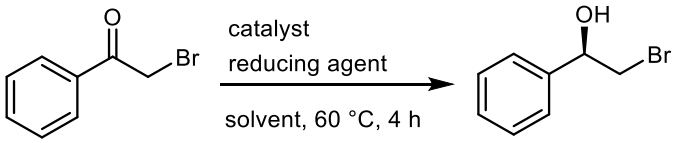
Table 1. ATH of **4a** using bifunctional DPEN-derived Ru catalysts.[a]

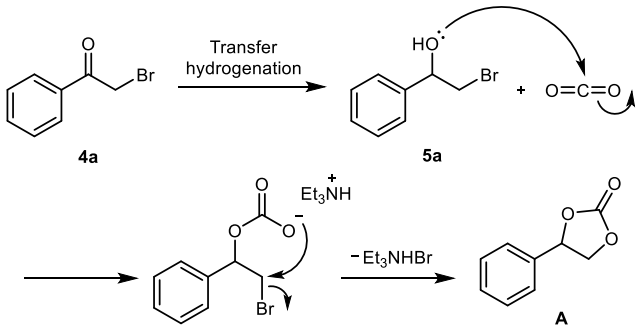


4a **5a**

Run	Catalyst	Reducing agent (equiv.)	Solvent	Conv. [%][b]	Select. for **5a** [%][b]	Ee [%][b]
1[c]	(*R*,*R*)-**1**	HCO_2H/Et_3N	-	100	trace	n.d.
2[c]	(*S*,*S*)-**2**	HCO_2H/Et_3N	-	100	4	87
3[c][d]	(*S*,*S*)-**2**	HCO_2H/Et_3N	EtOAc	100	6	97
4[c][d][e]	(*S*,*S*)-**2**	HCO_2H/Et_3N	EtOAc/H_2O	100	40	96
5[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	EtOAc/H_2O	100	98	95
6[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	BuOAc/H_2O	86	>99	95
7[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	toluene/H_2O	88	97	96
8[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	MeOH/H_2O	100	71	94
9[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	THF/H_2O	93	90	94
10[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(1)	$CHCl_3$/H_2O	100	>99	97
11[d][e]	(*S*,*S*)-**2**	HCO_2H(3)	EtOAc/H_2O	69	94	93
12[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(0.1)	EtOAc/H_2O	100	98	93
13[d][e]	(*S*,*S*)-**2**	HCO_2H(3)/HCO_2K(4)	EtOAc/H_2O	100	96	96
14[d][e]	(*S*,*S*)-**2**	HCO_2K(2)	EtOAc/H_2O	83	63	96

[a] Typical reaction conditions; substrate (5 mmol), ruthenium catalyst (S/C = 100 for (*R*,*R*)-**1** or S/C = 1000 for (*S*,*S*)-**2**).
[b] Determined by GC analysis using a CHIRALSIL-DEX-CB column.
[c] The amount of HCO_2H/Et_3N (5:2 azeotropic mixture) used was 2.5 mL.
[d] The amount of organic solvent used was 2.5 mL.
[e] The amount of H_2O used was 4 mL.

Scheme 2. Plausible mechanism of the formation of byproduct **A**.



This ATH system was also found to be applicable to 2-chloroacetophenone **6a** under similar conditions as the reaction of **4a** with S/C of 1000.[8c,10] As summarized in Table 2, the oxo-tethered catalyst bearing a Ms group, (*S*,*S*)-**3**, exhibited prominent catalytic performance identical to the Ts-substituted analog, (*S*,*S*)-**2**. Both substrates having an electron-donating group (run 3) and an electron withdrawing group (runs 2, 5 and 7) on the aromatic ring were converted to the corresponding (*R*)-alcohols in preferable enantioselectivities, whereas the *ortho*-fluorinated substrate **6f** provided a lower optical purity (run 6). Despite the electron-donating nature of the dimethylamino substituent on the aromatic ring, the ATH of **6h** required an extended reaction time of 8 h and resulted in a somewhat lower enantioselectivity (87% ee, run 8). When the catalyst amount was reduced to S/C = 5000, **6a** was successfully converted to the corresponding (*R*) alcohol with same selectivity and ee in a prolonged reaction time of 13.5 h (run 9).

Table 3 summarizes the substrate scope of α-bromoacetophenones for the HCO_2H/HCO_2K ATH system. In some cases (runs 4 and 5 in Table 3), slightly lower isolated yields were obtained for the reaction of **4d** and **4e**, compared with the results of the α-chloroacetophenone derivatives **6d** and **6e** in runs 4 and 5 of Table 2. The substrate with an electron withdrawing group on the aromatic ring resulted in a reduced optical purity (run 6), whereas electron-donating groups led to satisfactory results (runs 1-2, 4). Halogen atoms attached to the aromatic ring remained intact under the ATH conditions (runs 3, 7, and 9). These tendencies are similar to the outcomes of the α-chlorinated acetophenones in Table 2. It is striking that the unprecedented iodine-substituted substrates (**4i** and **6g**) and the corresponding products (**5i** and **7g**) did not deteriorate the catalyst performance.[11] A substrate with an ester group **4j** could also be chemoselectively transformed into the desired alcohol in a favorable isolated yield and enantioselectivity (run 10). In addition, the oxo-tethered Ru complexes were able to reduce aliphatic *tert*-butyl halomethyl ketones in good enantioselectivities of 50–70% (Table S1).[12]

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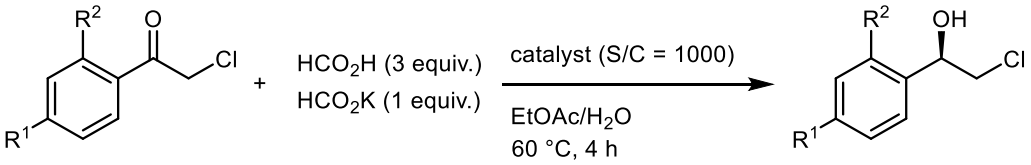
Table 2. ATH of 2-chloroacetophenone derivatives catalyzed by oxo-tethered Ru complexes.[a]



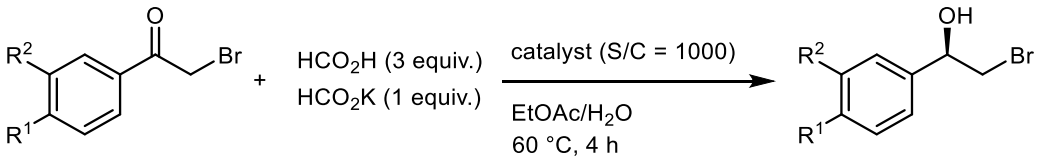
6a - 6i **7a - 7i**

conv. 100%

Run	Catalyst	R^1	R^2	Product	Isolated yield [%]	Ee [%]
1	(*S*,*S*)-**3**	-H	-H	**7a**	92	95[b] (*R*)
2	(*S*,*S*)-**3**	-Cl	-H	**7b**	94	93[b] (*R*)
3	(*S*,*S*)-**2**	-OMe	-H	**7c**	98	94[b] (*R*)
4	(*S*,*S*)-**2**	-Ph	-H	**7d**	94	95[b] (*R*)
5	(*S*,*S*)-**3**	-F	-H	**7e**	94	92[b] (*R*)
6	(*S*,*S*)-**3**	-F	-F	**7f**	92	79[b] (*R*)
7	(*S*,*S*)-**3**	-I	-H	**7g**	96	94[c] (*R*)
8[d]	(*S*,*S*)-**2**	-NMe_2	-H	**7h**	90	87[c] (–)
9[e]	(*S*,*S*)-**3**	-H	-H	**7a**	95	96[b] (*R*)

[a] Typical reaction conditions: substrate (5 mmol), EtOAc (2.5 mL), H_2O (4 mL).
[b] Determined by GC analysis using a CHIRALSIL-DEX-CB column.
[c] Determined by HPLC analysis.
[d] Reaction time = 8 h.
[e] Substrate (50 mmol), EtOAc (25 mL), H_2O (40 mL), S/C = 5000, 13.5 h.

Table 3. ATH of 2-bromoacetophenone derivatives catalyzed by oxo-tethered Ru complexes.[a]



4a - 4i **5a - 5i**

conv. 100%

Run	Catalyst	R^1	R^2	Product	Isolated yield [%]	Ee [%]
1	(*S*,*S*)-**2**	-H	-H	**5a**	93	96[b] (*R*)
2	(*S*,*S*)-**2**	-OMe	-H	**5b**	88	96[b] (*R*)
3	(*S*,*S*)-**2**	-Br	-H	**5c**	90	94[b] (*R*)
4	(*S*,*S*)-**3**	-Ph	-H	**5d**	86	97[b] (*R*)
5	(*S*,*S*)-**3**	-F	-H	**5e**	86	93[b] (*R*)
6	(*S*,*S*)-**3**	-H	-NO_2	**5f**	86	82[b] (*R*)
7	(*S*,*S*)-**2**	-Cl	-H	**5g**	92	93[b] (*R*)
8	(*S*,*S*)-**2**	-CF_3	-H	**5h**	94	94[b] (*R*)
9	(*S*,*S*)-**3**	-I	-H	**5i**	96	91[c] (*R*)
10[d]	(*S*,*S*)-**2**	-OAc	-H	**5j**	93	95[c] (–)

[a] Typical reaction conditions: substrate (5 mmol), EtOAc (2.5 mL), H_2O (4 mL).
[b] Determined by GC analysis using a CHIRALSIL-DEX-CB column.
[c] Determined by HPLC analysis.
[d] An elongated reaction time of 6 h.

The ATH of α-sulfonated acetophenones[10b,13] is also of interest because sulfonates substituents, such as mesylate and tosylate, are good leaving groups accessible to further transformations.[14] Nevertheless, the previous study has been confined to the use of expensive Rh catalysts bearing a bifunctional N-sulfonyl DPEN ligand. From the results shown in Scheme 3, these substrates could be hydrogenated successfully in similar high isolated yields and enantioselectivities even with a S/C ratio of 1000 as above demonstrated for the α-chloroacetophenone family.

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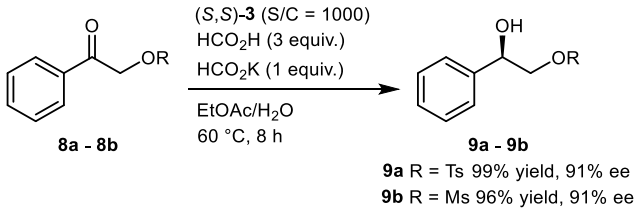
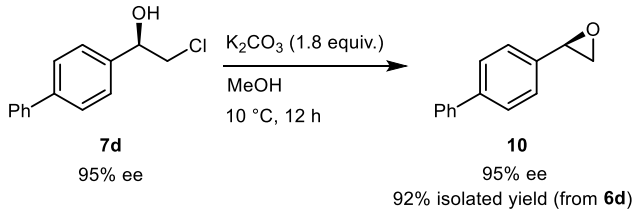
Scheme 3. ATH of α-sulfonated acetophenone derivatives.



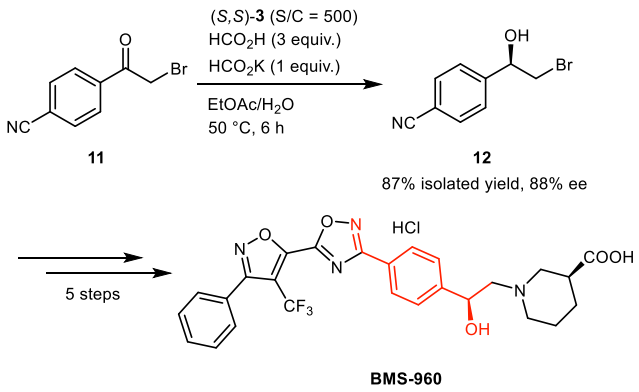
Regarding the derivatization of the obtained optically active haloalcohols, (*R*)-2-chloro-1-phenylethan-1-ol **7d** was completely converted into the corresponding chiral (*R*)-epoxide **10** which is convertible to various important chiral compounds such as 2-amino-1-alcohol[15a,b], β-azido alcohol[15b], and β-methoxy alcohol[15d] (Scheme 4).

Scheme 4. Derivatization of chiral α-chlorohydrin.



The catalytic ATH system also proved effective for the stereoselective synthetic route to BMS-960, a potent $S1P_1$ receptor agonist, as an alternative to the reported borane and enzymatic reaction[15c,e]. With slightly modified reaction conditions, the highlighted asymmetric reduction of bromomethyl 4-cyanophenyl ketone **11** with (*S*,*S*)-**3** afforded (*R*)-(–)-4-(2-bromo-1-hydroxyethyl)benzonitrile **12** in 87% isolated yield and 88% ee (Scheme 5). Unlike the biocatalytic and CBS reduction, the ATH system using the (*R*,*R*)-catalyst appropriate for the desired alcohol offers a highly reliable catalytic method free from the concerns of substrate specificity and generating equivalent amounts of boron waste.

Scheme 5. Synthesis of an intermediate to BMS960 by ATH.



In summary, we developed the effective ATH reaction system for α-substituted acetophenones, as typified by α-bromoketone derivatives. The oxo-tethered Ru complexes (*S*,*S*)-**2** and (*S*,*S*)-**3** served well as a catalyst in combination with HCO_2H/HCO_2K in aqueous EtOAc to provide a range of chiral secondary alcohols with useful functional groups accessible to further transformations. This ATH system is a more practical way to ensure extremely high selectivity than previously reported methods, associated with a significant reduction of the byproduct formation.

Experimental Section

Procedure for the asymmetric transfer hydrogenation of 2-bromoacetophenone 4a

To a 20-mL Schlenk tube, Ru complex (*S*,*S*)-**2** (3.3 mg, S/C = 1000), **4a** (995 mg, 5 mmol), HCO_2K (421 mg, 5 mmol), H_2O (4 mL), EtOAc (2.5 mL), and HCO_2H (0.57 mL, 15 mmol) were added under a N_2 atmosphere, and the mixture was stirred vigorously for 4 h at 60 °C. After completion of the reaction was confirmed by GC analysis, the reaction mixture was extracted with 5 mL of EtOAc three times. The combined organic layer was concentrated under vacuum, and then, the residue was purified by flash chromatography (hexane:EtOAc = 5:1) to afford the pure product **5a** in 93% yield.

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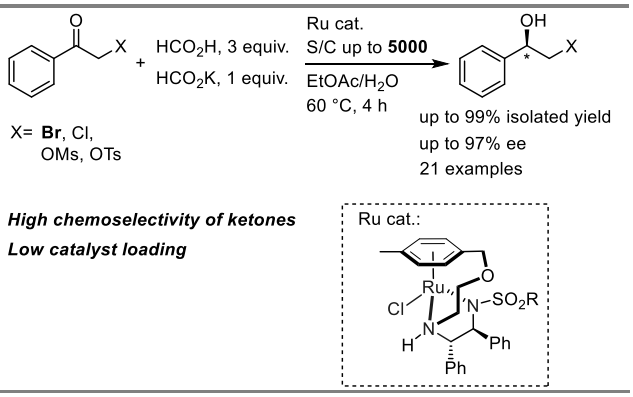

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