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Synthesis of Enantioenriched α,α-Dichloro- and α,α-Difluoro-β-Hydroxy Esters and Amides by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

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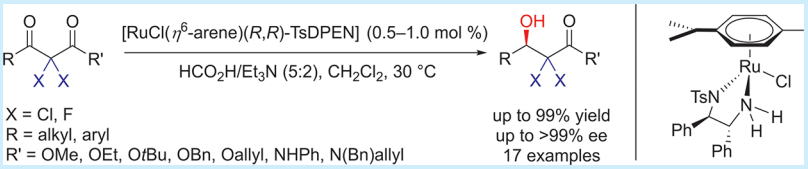
Supporting Information



ABSTRACT: A mild and convenient approach was developed to prepare a series of α,α-dihalogeno β-hydroxy esters or amides by using commercially available Noyori's complex [RuCl(*p*-cymene)(*R*,*R*)-TsDPEN] as a catalyst (S/C = 100−200) in the asymmetric transfer hydrogenation of the corresponding ketones. Moderate to high yields (up to 99%) and excellent enantioselectivities (up to >99% ee) were achieved for a series of variously substituted dichloro and difluoro β-hydroxy esters and amides.

Because of the ability of halogen atoms to improve oral absorption, blood-brain barrier permeability, or metabolic and chemical stability, halogenated compounds play a significant role in medicinal chemistry. The majority of the halogenated drugs approved by the FDA are fluorine and chlorine compounds,[1,2] and the introduction of a dichloromethylene or difluoromethylene fragment into bioactive molecules has created a new trend in drug discovery. Enantiomerically pure α,α-dichlorosubstituted or α,α-difluorosubstituted secondary alcohols are found in many biologically relevant molecules, such as statine analogues,[3a] a potent inhibitor of hepatitis C virus replication, β-D-2′-deoxy-2′-dichlorouridine prodrug,[3b] and the fluorinated Enigmol analogue CF_2-Enigmol, having enhanced antitumor activity.[3c] Alternatively, α,α-dichlorosubstituted or α,α-difluorosubstituted secondary alcohols can serve as valuable building blocks in medicinal chemistry as with 3,3-difluoropyrrolidin-4-ol[3d] (Figure 1).

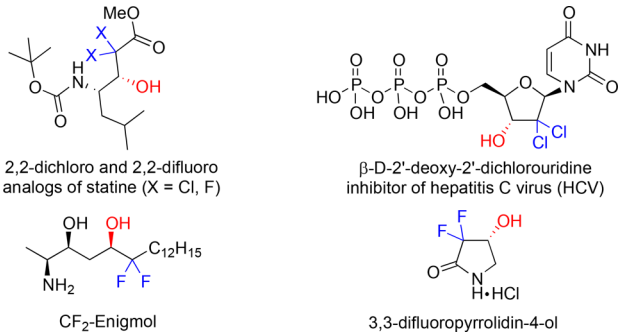


Figure 1. α,α-Dichloro- or α,α-difluoro-containing bioactive molecules.

Access to α,α-dichloro and α,α-difluoro β-hydroxyester derivatives has been reported through enzymatic[4a] or organocatalyzed[4b] kinetic resolution, as well as through enantioselective Mukaiyama aldol reactions.[4c−e] As far as asymmetric reduction of α,α-dihalogeno β-keto esters is concerned, rhodium- or ruthenium-catalyzed asymmetric hydrogenation[4f,g] and bioreduction[4h,i] have been described (Scheme 1).

These approaches mainly focused on difluorinated compounds and suffered from low yields in the case of kinetic resolution and bioreduction. As part of an ongoing program aimed at developing efficient methods for the asymmetric reduction of functionalized ketones,[5] we report herein the ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of α,α-dichloro and α,α-difluoro β-ketoester derivatives to access the corresponding dihalogenated alcohols efficiently in high yields and excellent enantioselectivies. The ATH of ketones has received significant attention in the past two decades, because it is one of the most powerful and useful methods for the generation of enantiomerically enriched secondary alcohols from the corresponding prochiral ketones, because of its high performance, in terms of activity and selectivity, and its operational simplicity.[6] Although the preparation of enantiomerically enriched CF_3,[7a−f] CCl_3[7g] or difluoro-substituted[7h−j] alcohols was described through ATH, to our knowledge, the ATH of α,α-dihalogenated β-ketoester derivatives has not been reported.[7k]

We first investigated the enantioselective reduction of benzyl 2,2-dichloro-3-oxobutanoate **1a** as a model reaction by using the tethered rhodium complex (*R*,*R*)-**3a** (0.5 mol %),[8] HCO_2H/Et_3N (5:2) azeotropic mixture as the hydrogen

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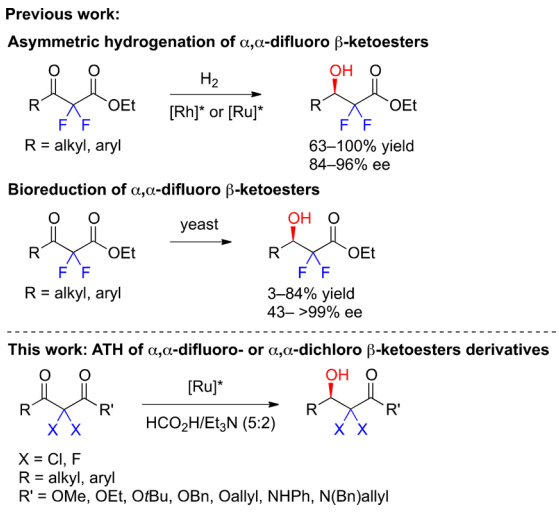
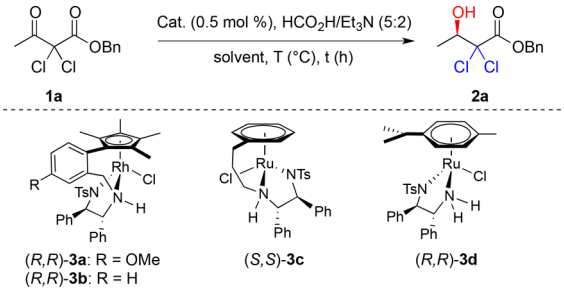
Scheme 1. Asymmetric Reduction of α,α-Dihalogeno β-Keto Esters



source, and CH_2Cl_2 as a solvent at 20 °C. Under these conditions, full conversion was achieved within 4 h and the corresponding alcohol (*R*)-**2a** was obtained in 77% yield with a high enantioselectivity (98% enantiomeric excess (ee); see Table 1, entry 1). Wills' tethered rhodium complex (*R,R*)-**3b**[9] afforded the same enantioinduction (98% ee) and a better yield (84% yield; see Table 1, entry 2). The catalyst screening also included tethered ruthenium complexes. Thus, (*S,S*)-**3c**[10] was used in the ATH of **1a** to give (*S*)-**2a** in 91% yield and 99% ee, albeit with a longer reaction time of 20 h (Table 1, entry 3). We also examined Noyori's catalyst (*R,R*)-**3d**,[11] [RuCl(*p*-cymene)(*R,R*)-TsDPEN], which gave similar results after 20 h (Table 1, entry 4). Interestingly, the reaction time was shortened to 5 h when the ATH was conducted at 40 °C, affording (*R*)-**2a** in 91% yield and >99% ee (Table 1, entry 5). An increase of the reaction concentration from 0.2 mol L^{-1} to 0.4 and 0.6 mol L^{-1} led to a faster reaction at 40 °C, but with a lower yield (87% or 83%, respectively; see Table 1, entries 6 and 7). We pursued the optimization of the reaction parameters by a solvent screening. Excellent ee values were obtained in EtOAc and THF after 17 h, albeit in lower yields, with only 92% conversion observed in the latter case (Table 1, entries 8 and 9). *i*-Pr_2O and *i*-PrOH were then investigated, giving full conversions within either 3 or 5 h, with 86% and 81% yields, respectively, and >99% ee (Table 1, entries 10 and 11). Dichloromethane therefore appeared as the more suitable solvent for this reaction and a slightly higher 96% yield could even be attained by running the reduction at 30 °C for 7 h instead of 40 °C (Table 1, entries 5 and 12). Based on the above screening, the optimized conditions were set as follows: (*R,R*)-**3d** (0.5 mol %) as the precatalyst, HCO_2H/Et_3N (5:2) (2.0 equiv), CH_2Cl_2 (0.2 M) at 30 °C.

Table 1. Optimization of Reaction Conditions for ATH of Benzyl 2,2-Dichloro-3-oxobutanoate (1a)[a]



entry	catalyst	solvent	temperature (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**	CH_2Cl_2	20	4	77	98
2	**3b**	CH_2Cl_2	20	5	84	98
3	**3c**	CH_2Cl_2	20	20	91	−99
4	**3d**	CH_2Cl_2	20	20	92	>99
5	**3d**	CH_2Cl_2	40	5	91	>99
6[d]	**3d**	CH_2Cl_2	40	3	87	>99
7[e]	**3d**	CH_2Cl_2	40	3	83	>99
8	**3d**	EtOAc	40	17	64	>99
9	**3d**	THF	40	17	67[f]	>99
10	**3d**	*i*Pr_2O	40	3	86	>99
11	**3d**	*i*PrOH	40	5	81	>99
12	**3d**	CH_2Cl_2	30	7	96	>99

[a]General conditions: **1a** (0.6 mmol), catalyst (0.006 mmol), HCO_2H/Et_3N (5:2) (101 μL), CH_2Cl_2 (3.0 mL). [b]Isolated yield, full conversion except where indicated. [c]Determined by SFC. [d][0.4 M]: CH_2Cl_2 (1.5 mL). [e][0.6 M]: CH_2Cl_2 (1.0 mL). [f]92% conversion.

With these optimized conditions in hand, we then investigated the scope of the Ru-catalyzed ATH of α,α-dihalogeno β-ketoester derivatives with a series of variously substituted dichloro and difluoro compounds **1a**−**1r** (see Table 2). The asymmetric reduction of compounds **1b**−**1d** bearing a benzyl ester and an alkyl ketone proceeded with longer reaction times (21−24 h), compared to the reaction with **1a**, and afforded alcohols **2b**−**2d** with excellent enantioselectivities, although a lower yield was obtained in the latter case, probably because of the more sterically demanding isobutyl substituent (Table 2, entries 2−4 vs entry 1). The *tert*-butyl and allyl ester analogues **1e** and **1f** of the standard substrate **1a**, were readily reduced to **2e** and **2f** with high levels of enantioselectivity (Table 2, entries 5 and 6). The ruthenium-mediated reduction of allyl, ethyl, or methyl ester derivatives **1g**, **1h**, and **1i** afforded the corresponding alcohols **2g** and **2h** in 98% and 72% yields, and 99% ee, whereas only traces of **2i** having a more hindered isopropyl substituent were detected (Table 2, entries 7−9). On the other hand, α,α-dichloro β-ketoester **1j** having a pentynyl substituent on the ketone was converted to **2j** in 76% yield and 98.5% ee (Table 2, entry 10). Although a high enantioselectivity was observed for the ATH of compound **1k** bearing a hexasubstituted benzene ring on the alkyl residue, the reaction proceeded with only 48% yield (Table 2, entry 11). Furthermore, the reduction of aromatic β-ketoesters **1l** and **1m** was also investigated. Both the yields and ee values were moderate for these substrates (Table 2, entries 12 and 13). In addition, fluorinated alkyl compounds were also evaluated and α,α-difluoro β-ketoesters **1n** and **1o** were efficiently reduced, even at room temperature, in excellent 99% yields and 98% ee (Table 2, entries 14 and 15). A quantitative yield was also obtained in the preparation of the benzyl alcohol derivative **2p**, although the ee was only moderate, as previously observed for the parent dichlorinated compound **2l** (Table 2, entries 16 and 12). Furthermore, the substrate scope was extended to α,α-dichloro β-keto amides with the ATH of compounds **1q** and **1r**. Thus, enantiomerically enriched *N*-phenyl-2,2-dichloro-3-hydroxybutanamide **2q** and *N*-allyl-*N*-benzyl-2,2-dichloro-3-hydroxybutanamide **2r** were readily prepared with high yields and ee values (Table 2, entries 17 and 18). The absolute

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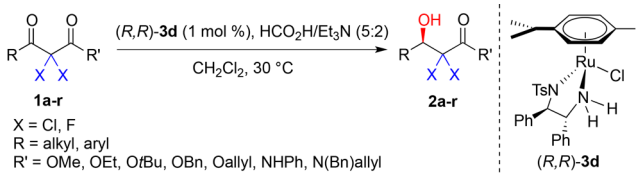
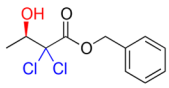
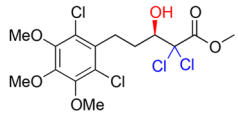
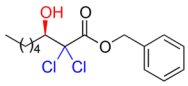
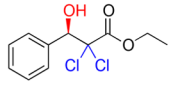
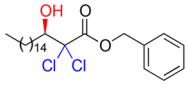
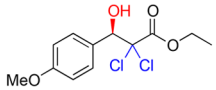
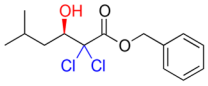
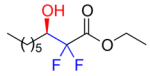
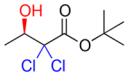
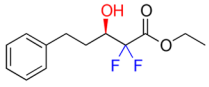
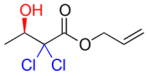
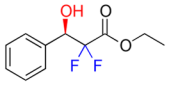
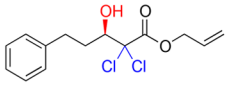
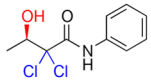
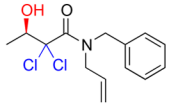
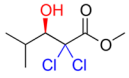
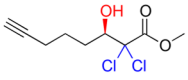
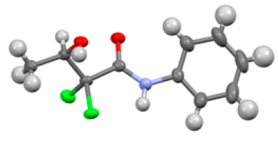
Table 2. ATH of α,α-Dichloro- and α,α-Difluoro-β-Keto Esters and Amides[a]



entry	product	time (h)	yield (%)[b]	ee (%)[c]	entry	product	time (h)	yield (%)[b]	ee (%)[c]
1	**2a** 	7	96	>99	11	**2k** 	24	48	98
2	**2b** 	22	70	>99	12	**2l** 	24	50	70
3	**2c** 	21	90	98	13	**2m** 	24	34	71
4	**2d** 	24	26[d]	>99	14[g]	**2n** 	5	99	98
5[e]	**2e** 	2.5	95	99	15[g]	**2o** 	13	99	98
6[e]	**2f** 	2.5	88	>99	16	**2p** 	5	99	56
7	**2g** 	8	98	99	17[e]	**2q** 	14	93	98.5
8	**2h** 	22	72	>99	18	**2r** 	3	99	98
9	**2i** 	22	--[f]	--[f]					
10	**2j** 	9	76	98.5					



X-ray crystallographic structure of **2q**

[a]Conditions: **1a−1r** (0.6 mmol), (*R*,*R*)-**3d** (0.006 mmol), CH_2Cl_2 (3.0 mL), HCO_2H/Et_3N (5:2) azeotropic mixture (101 μL), 30 °C. The reaction was monitored by TLC and/or ^1H NMR. [b]Isolated yield. [c]Determined by SFC or HPLC analysis. [d]51% conversion. [e]Reaction conducted on 1.0 mmol of **1** with 0.005 mmol of (*R*,*R*)-**3d**. [f]Traces of product **2i**, ee not measured. [g]Reaction performed at room temperature.

configuration of alcohol **2q** was unambiguously assigned as (*R*) by X-ray crystallographic analysis. In addition, comparison of the optical rotation value of compound **2p** with the reported literature data confirmed its (*R*) absolute configuration ($[\alpha]_D^{25}$ = −6.8 (c 1.0, $CHCl_3$), lit.[12] $[\alpha]_D^{24}$ = −13.4 (c 1.29, $CHCl_3$, 97% ee). By analogy, we conjecture that the remainder of the ATH products **2** followed the same trend.[13] In addition, a scale-up experiment was performed on compound **1a** (0.91 g, 3.48 mmol), using a lower catalyst loading of 0.5 mol %, and furnished the same yield and ee value as that observed on a 0.6 mmol scale (see Scheme 2). Furthermore, post-functionalization of **2f** and **2h** was studied. Thus, a cross metathesis between allyl (*R*)-2,2-dichloro-3-hydroxybutanoate **2f** and 1-octene using Grubbs II catalyst allowed formation of alkene **4** in 67% yield as a 5.8:1 mixture of *E* and *Z* isomers. On the other hand, ethyl (*R*)-2,2-dichloro-3-hydroxyhexanoate **2h** was readily converted into the corresponding β-hydroxy Weinreb amide **5** in the presence of *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in 85% yield. The amide could then serve as a ketone precursor and was, for instance, transformed to the phenyl ketone **6** via treatment with phenylmagnesium chloride (see Scheme 2).

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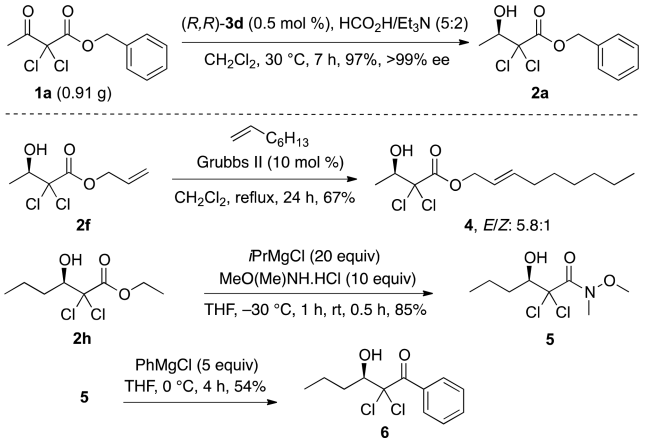
Scheme 2. Scale-Up Experiment and Post-functionalization Reactions



In conclusion, highly enantiomerically enriched α,α-dichloro or α,α-difluoro β-hydroxy esters and β-hydroxy amides can be prepared through ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of the corresponding ketones under mild conditions. The use of commercially available precatalyst [RuCl(*p*-cymene)(*R*,*R*)-TsDPEN] (S/C = 100−200) in the presence of formic acid/triethylamine (5:2) as the hydrogen source allowed the efficient reduction of a wide range of nonaromatic α,α-dihalogeno β-keto esters in good to high yields (up to 99% yield) and with excellent enantioselectivities (up to >99% ee), whereas aromatic derivatives led to fair ee values. The reaction was tolerant of various esters, as well as being applicable to amides. Moreover, the ATH was efficiently performed on gram-scale with compound **1a**, demonstrating the usefulness of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01943.

Experimental procedures, compound characterization data, NMR spectra and HPLC or SCF data for all new compounds (PDF)

Accession Codes

CCDC 1850872 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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