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Asymmetric Hydrogenation of α-Chloro Aromatic Ketones Catalyzed by η^6-Arene/TsDPEN–Ruthenium(II) Complexes

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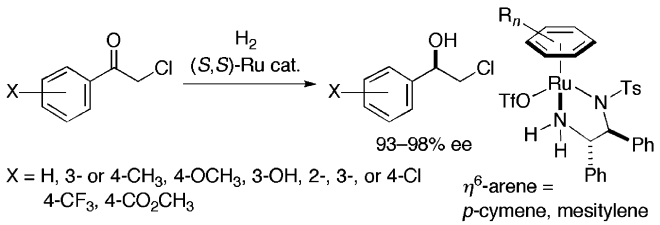
ABSTRACT



Asymmetric hydrogenation of various α-chloro aromatic ketones with Ru(OTf)(TsDPEN)(η^6-arene) (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) produces the chiral chlorohydrins in up to 98% ee. This reaction can be conducted even on a 206-g scale. The hydrogenation of an α-chloro ketone with a phenol moiety has been utilized for the synthesis of (*R*)-norphenylephrine without protection–deprotection operations.

Optically active chlorohydrins are versatile intermediates for the syntheses of biologically active compounds, including *β*-amino alcohols,[1,2] substituted pyrrolidines,[3] and a functionalized cyclopropane compound.[4] Asymmetric reduction of the α-chloro ketones is a straightforward method to produce this important class of compounds. Hydroboration catalyzed by chiral oxazaborolidines[1−3,5] and transfer hydrogenation with chiral Rh[6] and Ru[7] catalysts show excellent

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enantioselectivity for a variety of α-chloroacetophenone derivatives. Despite the fruitful results of these asymmetric reactions, to our knowledge no reliable catalyst for asymmetric hydrogenation of α-chloro ketones exists.[8] We previously exploited $RuCl_2$(binap)(1,2-diamine)[9−11] and RuH(η^1-BH_4)(binap)(1,2-diamine)[11,12] complexes, which show excellent activity and enantioselectivity for hydrogenation of simple aromatic, heteroaromatic, α-amino, and α,β-unsaturated ketones under basic or slightly basic conditions. However, these catalyst systems cannot be applied to the reaction of highly base-labile α-chloro ketones.[13] We recently reported that Ru(OTf)(TsDPEN)(η^6-*p*-cymene) (**3a**) (TfO^- = trifluoromethanesulfonate, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) in methanol efficiently catalyzes asymmetric hydrogenation of 4-chromanones, which are another type of base-sensitive ketonic substrates.[14] The neutral to slightly acidic conditions fit the requirement of this reaction. We describe here enantioselective hydrogenation of α-chloro aromatic ketones catalyzed by the η^6-arene/TsDPEN−Ru(II) complexes.[15] A series of chiral chlorohydrins are obtained quantitatively in excellent enantiomeric excess (ee). This reaction can be conducted even on a practical (206-g) scale.

Our previous mechanistic studies on hydrogenation of ketones with RuX(TsDPEN)(η^6-*p*-cymene) complexes (**3a**, X = OTf; **3b**, X = Cl) revealed that the generation of cationic Ru(II) species, [Ru(TsDPEN)(η^6-*p*-cymene)]$^+$, is crucially important to achieve high catalytic activity.[14,16] This is because molecular H_2 is activated on the cationic Ru center, producing a catalytic species, RuH(TsDPEN)(η^6-*p*-cymene), with release of H^+. A highly polarized Ru triflate **3a** is smoothly ionized in a methanol solution, supplying the active Ru cationic species. Thus, we selected **3a** as a precatalyst for asymmetric hydrogenation of α-chloro aromatic ketones. When α-chloroacetophenone (**1a**) (206 g) and (*S*,*S*)-**3a** (1.02 g) (substrate/catalyst molar ratio (S/C) = 1000) in methanol (5.3 L) was stirred under 10 atm of H_2 at 30 °C for 10 h in a stainless steel autoclave, (*R*)-2-chloro-1-phenylethanol [(*R*)-**2a**] in 96% ee was quantitatively produced (Scheme 1 and Table 1). Methanol was the solvent of choice. Use of ethanol or 2-propanol as a solvent instead of methanol reduced both the reactivity and enantioselectivity.[14] The coordinative α-chloro functionality of the substrate did not prevent the catalyst performance. Complete conversion within 15 h in the reactions with an S/C of 2000 and 4000 was achieved under 20 and 100 atm of H_2, respectively. When the reaction with (*S*,*S*)-**3a** (S/C = 2000) was conducted under 10 atm of H_2 at 30 °C for 15 h, (*R*)-**2a** in 96% ee was obtained in 73% yield (Table 1). Under the same conditions, only 21% yield of the alcohol was attained by use of the less-polarized Ru chloride **3b** as a precatalyst, while the enantioselectivity was also high. Addition of an electrolyte, $NaClO_4$, did not help increase the catalytic activity of **3b** (Table 1). The reaction with the mesitylene−Ru complex **3c** in place of the *p*-cymene−Ru complex **3a** achieved a higher enantioselectivity of 98%.

A series of α-chloroacetophenones **1** substituted on the phenyl rings were hydrogenated with the η^6-arene/TsDPEN−Ru(II) triflates, **3a** and **3c**, in methanol to afford quantitatively the chlorohydrins **2** with consistently high enantioselectivity (Table 1). Thus, hydrogenation of 3′-CH_3-substituted ketone **1b** in the presence of (*S*,*S*)-**3a** with an S/C of 1000 under 10 atm of H_2 at 30 °C for 15 h gave (*R*)-**2b** in 96% ee and 98% yield. The 4′-CH_3-substituted ketone **1c** was hydrogenated in the same manner. Substitution of an electron-donating CH_3O group at the 4′ position (**1d**) slightly lowered the reactivity, while the enantioselectivity was not influenced by the substitution. Thanks to the nonbasic reaction condi-

Scheme 1

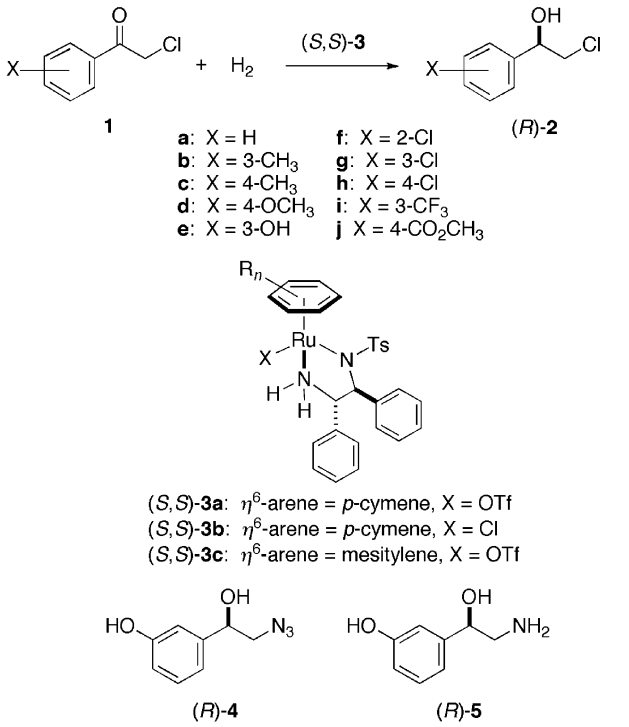

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Table 1. Asymmetric Hydrogenation of α-Chloro Ketones[a]

ketone		conditions				*R* alcohol[b]	
no.	Ru cat. no.	$[\mathbf{1}]_0$ [M][c]	S/C[d]	H_2 [atm]	time [h]	yield [%][e]	ee [%][e]
1a[f]	(*S*,*S*)-**3a**	0.25	1000	10	10	>99	96
1a	(*S*,*S*)-**3a**	0.47	2000	10	15	73	96
1a	(*S*,*S*)-**3a**[g]	0.50	2000	20	15	>99	95
1a	(*S*,*S*)-**3a**	1.00	4000	100	15	>99	95
1a	(*S*,*S*)-**3b**	0.47	2000	10	15	21	96
1a	(*S*,*S*)-**3b**[h]	0.47	2000	10	15	25	95
1a	(*S*,*S*)-**3c**	0.25	1000	10	16	>99	98
1b	(*S*,*S*)-**3a**	0.25	1000	10	15	98	96
1c	(*S*,*S*)-**3a**	0.25	1000	10	15	>99	95
1d	(*S*,*S*)-**3a**	0.25	1000	10	20	99	95
1e	(*S*,*S*)-**3a**	0.25	1000	10	15	>99	96
1e	(*S*,*S*)-**3c**	0.25	1000	10	15	>99	98
1f	(*S*,*S*)-**3a**	0.13	500	10	15	>99	95
1g	(*S*,*S*)-**3a**	0.25	1000	10	15	>99	94
1h	(*S*,*S*)-**3a**	0.25	1000	10	15	>99	93
1h	(*S*,*S*)-**3c**	0.25	1000	10	15	>99	96
1i	(*S*,*S*)-**3a**	0.13	500	10	15	>99	93
1j	(*S*,*S*)-**3a**	0.25	1000	10	15	>99	94

[a] Unless otherwise stated, reactions were conducted in methanol containing 1.5 μmol of **3** (0.25 mM) at 30 °C in a silanized glass (10 atm) or stainless steel (>20 atm) autoclave. [b] *R* alcohols were obtained in all cases. See Supporting Information. [c] Initial concentration of ketones **1**. [d] Substrate/catalyst molar ratio. [e] Determined by chiral GC and/or HPLC analysis. [f] A 206 g-scale reaction in 5.3 L of methanol in a 20-L stainless steel autoclave. [g] Reaction using 4.5 μmol of **3a**. [h] Fifty equiv of $NaClO_4$ was added to the Ru catalyst.

tions, a ketonic substrate **1e** with a phenolic hydroxyl group was completely converted to the chiral alcohol **2e** in 96% ee without protection. The reaction with **3c** resulted in an even better optical yield of 98%. The phenolic chlorohydrin, (*R*)-**2e**, was easily converted to (*R*)-norphenylephrine [(*R*)-**5**][17] through the β-azido alcohol, (*R*)-**4**, without protection−deprotection processes (conditions: (a) 5 equiv of NaN_3, DMF, 100 °C, 8 h; (b) 1 atm of H_2, Pd/C catalyst, methanol, 25 °C, 15 h).[18] The Cl-substituted ketones at the 2′, 3′, and 4′ positions, **1f**−**1h**, were hydrogenated with (*S*,*S*)-**3a** to afford (*R*)-**2f**−**2h** in the range 93−95% ee. The reactivity of the 2′-substituted ketone **1f** was relatively lower than that of the 3′- and 4′-substituted ketones, **1g** and **1h**. The chiral chlorohydrin **2h** in a higher ee of 96% was obtained by hydrogenation with the mesitylene−Ru complex **3c**. The chiral chlorohydrins, (*R*)-**2f** and (*R*)-**2g**, are convertible to β-adrenoceptor agonists, including (*R*)-tulobuterol,[19] CL316243,[2c] FK175,[20] and SR58611A.[8,21] The substrate **1i** with a strongly electron-withdrawing CF_3 group at the 3′ position was reduced with **3a** to produce quantitatively the chiral alcohol **2i** in 93% ee. The hydrogenation tolerated the CO_2CH_3 moiety, so that **1j** was completely converted to **2j** in 94% ee without loss of functionality.

In conclusion, we report here the first example of highly enantioselective hydrogenation of α-chloro aromatic ketones with the η^6-arene/TsDPEN−Ru(II) triflates, **3a** and **3c**. Even 206 g of substrate is completely converted to the desired chiral alcohol. Synthetically useful chiral chlorohydrins are quantitatively produced in up to 98% ee by this method. The hydrogenation tolerates phenolic OH and CO_2CH_3 functionalities. A phenol-substituted β-amino alcohol, (*R*)-norphenylephrine, is synthesized by means of this reaction without use of protective groups. Thus, this method provides a practical tool for stereoselective organic synthesis.

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Supporting Information Available: Preparative methods and properties of the chiral Ru complex **3c**, procedures for asymmetric hydrogenation of α-chloro aromatic ketones, NMR, GC, and HPLC behavior of products, together with $[\alpha]_D$ values and absolute configuration determinations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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