Asymmetric Hydrogenation of 2-Arylated Cycloalkanones through Dynamic Kinetic Resolution

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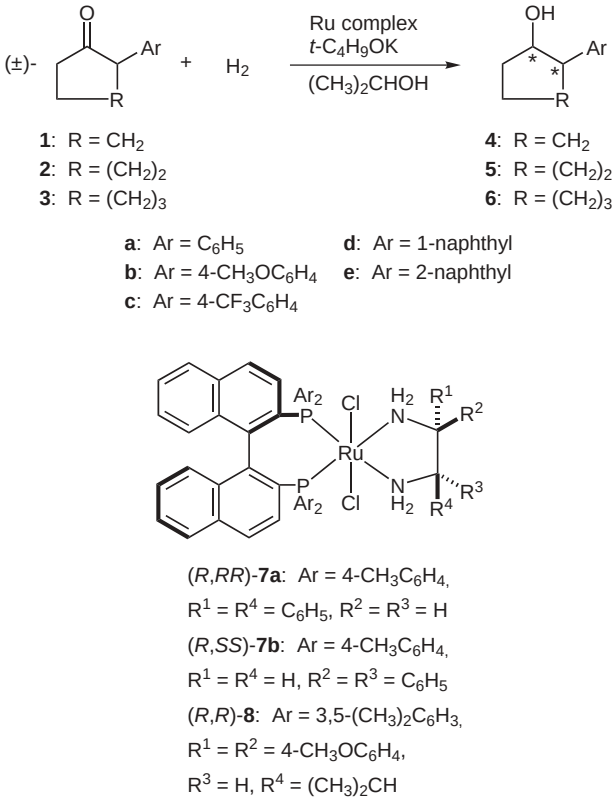
Dedicated to Professor Clayton H. Heathcock in recognition of his significant contribution to organic synthesis and basic science.

Abstract: Asymmetric hydrogenation of 2-arylcycloalkanones with *trans*-$RuCl_2$(binap)(1,2-diamine) and *t*-C_4H_9OK in 2-propanol selectively gives the corresponding *cis*-2-arylcycloalkanols in excellent enantiomeric purity and high yield. Two synthetic intermediates of biologically active compounds have been prepared by this method.

Key words: 2-arylcycloalkanones, asymmetric hydrogenation, BINAP, dynamic kinetic resolution, ruthenium complexes

Under suitable conditions, asymmetric hydrogenation of certain configurationally labile chiral ketones can lead to single isomeric alcohols out of four possible stereoisomers.[1,2] Thus hydrogenation of a racemic α-substituted ketone with $RuCl_2$(binap)(1,2-diamine)[3,4] and an alkaline base in 2-propanol gives a single chiral alcohol selectively and in high yield.[5–7] In this reaction, a chiral Ru hydride species generated from the $RuCl_2$ precatalyst reduces a ketone enantiomer (kinetic resolution) selectively with a high *cis*:*trans* diastereoselectivity. The slow-reacting ketone enantiomer is facilely racemized due to the protic basic conditions and both enantiomers consequently serve as hydrogenation substrates. We describe here the enantio- and diastereoselective hydrogenation of 2-arylcycloalkanones (**1**–**3**) to *cis*-2-arylcyclohexanols (**4**–**6**) of high enantiomeric purity under dynamic kinetic resolution (Scheme 1).[1,8] In addition, this method has been applied to the synthesis of certain important chiral building blocks.



Scheme 1

First, we selected 2-phenylcyclohexanone (**2a**) as a standard substrate. When racemic **2a** was hydrogenated in 2-propanol containing *trans*-$RuCl_2$[(*R*)-tolbinap][(*R*,*R*)-dpen] [(*R*,*RR*)-**7a**][4d] and *t*-C_4H_9OK {[**2a**] = 0.5 M, [*t*-C_4H_9OK] = 15 mM, ketone:Ru = 10,000:1} at 8 atm of H_2 and 25 °C for 24 hours, (1*S*,2*S*)-2-phenylcyclohexanol [(1*S*,2*S*)-**5a**] was obtained in 99.7% ee and 100% yield. The *cis* diastereoselectivity was perfect. The bulky RuH(diamine) intermediate delivers a hydride on Ru and a proton on nitrogen to the carbonyl function via a six-membered pericyclic transition state.[9] As illustrated in Scheme 2, the (*R*)-BINAP–(*R*,*R*)-DPEN-combined complex kinetically selects (*S*)-**2a** with its stable chair conformer possessing an equatorial phenyl substituent, and approaches the C=O function from the equatorial direction,[10] resulting in the 1*S*,2*S*-product. This reaction is highly productive. Thus, the reaction of 9.12 g of **2a** using 0.5 mg of (*R*,*RR*)-**7a**, viz., substrate:catalyst = 100,000:1, at 8 atm of H_2 and 25 °C was completed in 48 hours to quantitatively afford (1*S*,2*S*)-**5a** in 99.6% ee.[11] The diastereomeric (*R*)-TolBINAP–(*S*,*S*)-DPEN-based Ru complex, (*R*,*SS*)-**7b**, is even more active than (*R*,*RR*)-**7a** but slightly less stereoselective, giving (1*S*,2*S*)-**5a** in 97% ee.

Various 2-arylated cyclohexanones can be used consistently, although the extent of enantio- and/or diastereoselectivity is influenced by the substituents, as exemplified in Table 1. Hydrogenation of the *p*-methoxyphenyl derivative **2b** in the presence of (*R*,*RR*)-**7a** resulted (1*S*,2*S*)-**5b** in 99.5% ee and 100% *cis* selectivity, while the *p*-trifluoromethylphenyl analogue **2c** gave (1*S*,2*S*)-**5c** with a lower stereoselectivity (98% ee, 99.9% *cis*) under similar reaction conditions.[12] Hydrogenation of 2-(2′-naphthyl)cyclohexanone (**2e**) with (*R*,*RR*)-**7a** afforded (1*S*,2*S*)-**5e** in

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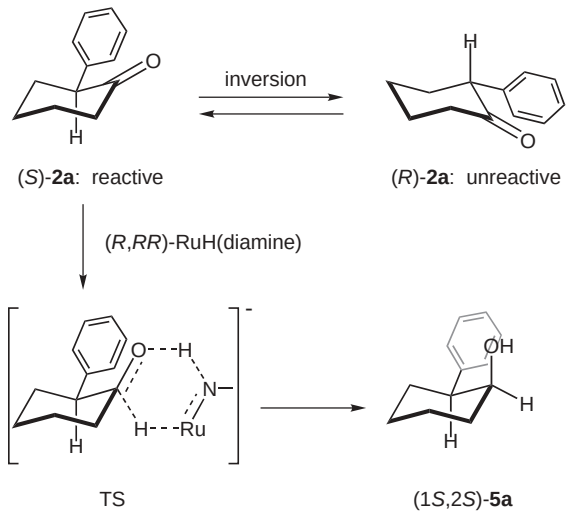

Scheme 2

>99% ee and a *cis*:*trans* selectivity of >99:1,[12] but the reaction of the 1′-naphthyl derivative **2d** proceeded less stereoselectively to give (1*S*,2*S*)-**5d** in 93% ee and with a *cis*:*trans* selectivity of 98:2, due to changes in the steric parameters.

The skeletal change in ketonic substrates requires the modification of the catalyst structures (Table 1). Hydrogenation of 2-phenylcycloheptanone (**3a**) under the standard conditions using (*R*,*RR*)-**7a** (ketone:Ru = 2000:1, 8 atm, 25 °C, 27 h) gave (1*S*,2*S*)-2-phenylcycloheptanol [(1*S*,2*S*)-**6a**] in only 84% ee and 90% yield, albeit with perfect *cis* selectivity.[12] However, the enantioselectivity and rate were significantly enhanced by the use of diastereomeric (*R*,*SS*)-**7b** as a precatalyst, resulting in (*S*,*S*)-**6a** (100% *cis*) with 95% ee and 100% yield after 24 hour reaction. Hydrogenation of the lower homologue, 2-phenylcyclopentanone (**1a**), with (*R*,*RR*)-**7a** or (*R*,*SS*)-**7b** (ketone:Ru = 2000:1, 8 atm, 25 °C, 36–48 h) gave (1*S*,2*S*)-2-phenylcyclopentanol [(1*S*,2*S*)-**4a**] in 80% ee (*cis*:*trans* = 94.5:5.5) and 76% ee (*cis*:*trans* = 100:0), respectively. Fortunately, however, when an (*R*)-XylBINAP–(*R*)-DAIPEN-based Ru complex [(*R*,*R*)-**8**][3,4e] was used, the 1*S*,2*S*-alcohol was obtained in 98% ee and 100% *cis* selectivity.

Notably, this asymmetric hydrogenation under dynamic kinetic resolution is applicable to ketonic substrates possessing an azacyclohexanone skeleton (Figure 1). Thus, the hydrogenation of **9**[13] with (*R*,*RR*)-**7a** and *t*-C_4H_9OK in 2-propanol {[**9**] = 0.125 M, [*t*-C_4H_9OK] = 19 mM, ketone:Ru = 500:1, 8 atm, 20 h} produced (2*S*,3*S*)-**10** in 96% ee and quantitative yield with a 96:4 *cis*:*trans* selectivity {$[\alpha]_D^{25}$ +29.9 (*c* 0.39, CH_3OH)}.[14] This chiral alcohol is convertible to the hNK_1 antagonists L-733,060[15] and L-741,671.[16] Furthermore, the *m*-methoxyphenyl ketone **11**[17] was hydrogenated with (*S*,*SS*)-**7a** {[**11**] = 0.125 M, [*t*-C_4H_9OK] = 25 mM, ketone:Ru = 500:1, 8 atm, 25 °C, 24 h} quantitatively and stereoselectively to (3*S*,4*R*)-**12** in 97% ee with a *cis*:*trans* selectivity of >99:1 {$[\alpha]_D^{25}$ –55.9 (*c* 0.40, CH_3OH)}.[12] This product serves as a synthetic intermediate of (–)-precramol, which is known as a D_2/D_3-auto and sigma receptor agonist.[18]

Table 1 Asymmetric Hydrogenation of Racemic 2-Arylated Cycloalkanones **1**–**3**[a]

		Conditions			Alcohol				
								cis-Isomer	
Ketone	Complex	Ketone:Ru	[*t*-C_4H_9OK] (mM)	Time (h)	Yield[b] (%)	*cis*:*trans*[b]	ee (%)[c]	Config.[d]	$[\alpha]_D$ (°)[e]
1a	(*R*,*R*)-**8**	2,000:1	50	96	100	100:0	98	1*S*,2*S*	+79.8 (*c* 1.01)
2a	(*R*,*RR*)-**7a**	10,000:1	15	24	100	100:0	99.7	1*S*,2*S*	–
2a[g]	(*R*,*RR*)-**7a**	100,000:1	18	48	100	100:0	99.6	1*S*,2*S*	+103.6 (*c* 2.02)[f]
2a	(*R*,*SS*)-**7b**	2,000:1	25	4	99.6	100:0	97	1*S*,2*S*	–
2b	(*R*,*RR*)-**7a**	2,000:1	5	4	100	100:0	99.5	1*S*,2*S*[h]	+85.0 (*c* 1.60)
2c	(*R*,*RR*)-**7a**	2,000:1	6	4	99.9	99.9:0.1	98	1*S*,2*S*[h]	+59.6 (*c* 0.30)
2d	(*R*,*RR*)-**7a**	2,000:1	9	16	>99	98:2	93	1*S*,2*S*	+145.0 (*c* 0.90)
2e	(*R*,*RR*)-**7a**	2,000:1	10	4	>99	>99:1	>99	1*S*,2*S*[h]	+47.4 (*c* 0.20)
3a	(*R*,*SS*)-**7b**	2,000:1	25	24	100	100:0	95	1*S*,2*S*[h]	+93.3 (*c* 0.21)

[a] Reactions were conducted at 25 °C under 8 atm of H_2 using a 0.5 M solution of the ketone in 2-propanol.
[b] Determined by GC, HPLC, and ^1H NMR analysis.
[c] Determined by chiral GC or HPLC analysis.
[d] Determined by the sign of rotation.
[e] A *cis*-alcohol purified using a silica-gel column. Measured in $CHCl_3$ at 22–24 °C.
[f] Measured in CH_3OH.
[g] Reaction using 9.12 g of **2a** in 100 mL of 2-propanol.
[h] Estimated by ^1H NMR measurement after conversion to diastereomeric compounds according to ref.[12]

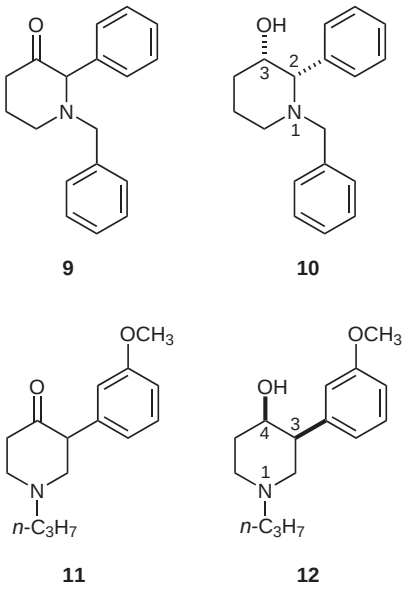

Figure 1

Thus, the asymmetric hydrogenation of racemic 2-arylcycloalkanones through dynamic kinetic resolution, when coupled with previous methods, provides a practical tool for the synthesis of *cis*-2-subsitituted cycloalkanols and aza-analogues of high enantiomeric purity, which are otherwise difficult to prepare. The optimum conditions are obtained by the careful selection of structural parameters in the BINAP–diamine Ru catalysts. The reaction is achievable with low catalyst loading (ketone:Ru ratio of up to 100,000:1) and under relatively low hydrogen pressure (8 atm) at room temperature.

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Solid (*R*,*RR*)-**7a** (0.5 mg, 0.47 μmol), *t*-C_4H_9OK (180 mg, 1.73 mmol), and **2a** (9.12 g, 51.2 mmol) were placed in a 500 mL glass autoclave equipped with a Teflon-coated magnetic stirring bar. Air present in the autoclave was replaced by argon. 2-Propanol (100 mL), which had been degassed by three freeze-thaw cycles, was added to the autoclave. The vessel was pressurized to 8 atm of hydrogen. The reaction mixture was vigorously stirred at 25 °C for 48 h, during which time the hydrogen cylinder was kept connected. After carefully venting the hydrogen gas in the apparatus, the solvent was removed under reduced pressure. The yield determined by GC was 100%. Subsequently, the residue was passed through a silica gel pad, eluted with a 1:4 EtOAc–hexane mixture giving (1*S*,2*S*)-**5a** (8.61 g, 93% yield, *cis*:*trans* = 100:0, 99.6% ee), $[\alpha]_D^{23}$ +103.6 (*c* 2.02, CH_3OH) {lit. $[\alpha]_D^{27}$ –106 (*c* 0.20, CH_3OH)}, 1*R*,2*R*-Isomer: Verbit, L.; Price, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 5143.

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