One-Pot Sequential Asymmetric Hydrogenation Utilizing Rh(I) and Ru(II) Catalysts

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4-Amino-3-hydroxy-5-phenylpentanoic acid (AHPPA),[1] an analogue of statine,[2] has been utilized as a transition-state analogue of peptide hydrolysis for aspartic proteases (i.e., HIV protease) and as a key component for the development of inhibitors of those proteases.[3] As such, the ability to exclusively prepare both enantiomers of the two possible diastereomers of phenyl-substituted AHPPA analogues from the same molecule by a simple manipulation would be beneficial for the preparation of chemical libraries containing various statine analogues that could be used in drug discovery. Asymmetric hydrogenation using a homogeneous catalyst with a chiral phosphine ligand is attractive in this regard, in that either enantiomer can be easily prepared using an enantiomerically pure phosphine ligand. Herein, we wish to report a one-pot sequential asymmetric hydrogenation of γ-(acylamino)-γ,δ-unsaturated-β-keto esters **1** that provides the two possible statine analogues **2** and **3**, respectively, in enantiomerically pure form, in the presence of both Rh(I)− and Ru(II)−chiral phosphine complexes.[4]

Although the asymmetric hydrogenation of dehydroamino acids and β-keto esters catalyzed by Rh(I)−[5] and Ru(II)−chiral phosphine[6] complexes has been extensively investigated,[7] that of α-(acylamino) unsaturated ketones is rare.[8] We first examined the asymmetric hydrogenation of the alkene moiety of γ-(acylamino)-γ,δ-unsaturated-β-keto esters **1** (step a in Scheme 1). The results are depicted in Table 1. Asymmetric hydrogenation of the alkene moiety in **1a** took place exclusively (1 equiv of NEt_3 in EtOH/40 °C/24 h) when rhodium−phosphine complexes were used as catalysts (1 mol %). With [Rh(COD)(*S*)-BINAP]$^+ClO_4^-$,[9] the product (*R*)-**4a** was obtained quantitatively in 99% ee (Entry 1). The reactions catalyzed by [Rh(COD)(*S*,*S*)-DIOP]$^+ClO_4^-$ and [Rh(COD)[(*R*,*R*)-Me-DuPHOS]$^+ClO_4^-$ gave (*S*)-**4a** and (*R*)-**4a** with 50% and 99% ees, respectively (Table 1, entries 3 and 5).[10,11] The chiral induction decreased dramatically in the absence of triethylamine under 30 atm of hydrogen (entries 2 and 4).[12] It is conceivable that enolization of **1a** in the presence of triethylamine accelerates the coordination of the substrate to a rhodium species leading to enhanced chiral induction. In all cases, the sense of the chiral induction in the present hydrogenation is the same as that observed in the asymmetric hydrogenation of α-(acylamino)-cinnamic acids using the corresponding catalyst.[7] Subsequent reduction of β-keto ester (*R*)-**4a**, catalyzed by $RuBr_2$-[(*S*)-BINAP],[6,13] paralleled the previous report,[14] except for the presence of triethylamine, giving (3*R*,4*R*)-**2a** in quantitative yield with >95% de (step b).

Since the stepwise reduction of **1a** gave satisfactory results (steps a and b in Scheme 1), the one-pot sequential

Scheme 1. Hydrogenation of Alkene and Ketone in 1

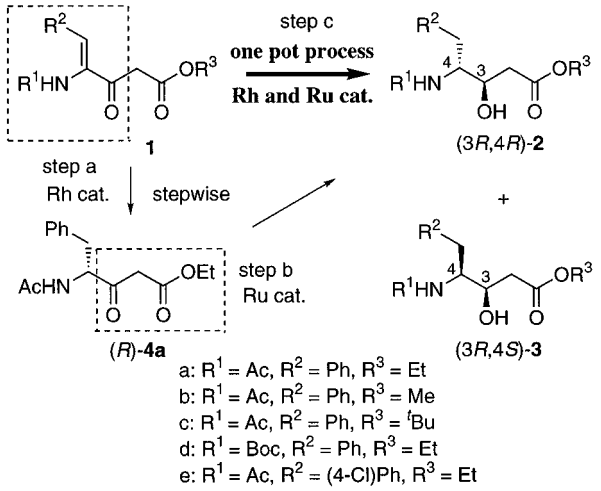

Table 1. Rh(I)-Catalyzed Asymmetric Hydrogenation of 1a to 4a[a]

entry	catalyst	H_2, atm	additive	yield, %	ee,[b] %
1	[Rh(COD)(*S*)-BINAP]$^+ClO_4^-$	10	NEt_3	100	>99 (*R*)
2	[Rh(COD)(*S*)-BINAP]$^+ClO_4^-$	30	none	100	50 (*R*)
3	[Rh(COD)(*S*,*S*)-DIOP]$^+ClO_4^-$	10	NEt_3	100	50 (*S*)
4	[Rh(COD)(*S*,*S*)-DIOP]$^+ClO_4^-$	30	none	100	33 (*S*)
5	[Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+ClO_4^-$	10	NEt_3	100	>99 (*R*)

[a] The reaction was carried out using 1 mol % of Rh(I)-catalyst in ethanol at 40 °C for 24 h. [b] The enantiomeric excess was determined by HPLC (CHIRALCEL OD) and capillary GC (CHROMPACK). BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DIOP = diisopropylidene dihydroxy-2,3-bis(diphenylphosphino)-1,4-butane; Me-DuPHOS = 1,2-bis(*trans*-2,5-dimethylphospholano)benzene.

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Table 2. One-Pot Sequential Asymmetric Hydrogenation of 1 to 2 and 3 Catalyzed by Both Rh(I) and Ru(II) Catalysts[a]

			yield, % (ee, %)[b]	
entry	compd	catalysts	(3*R*,4*R*)-**2**	(3*R*,4*S*)-**3**
1	**1a**	Rh[(COD)(*S*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	**2a** 99 (>95)	
2	**1b**	Rh[(COD)(*S*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	**2b** 99 (>95)	
3	**1c**	Rh[(COD)(*S*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	no reaction	
4	**1d**	Rh[(COD)(*S*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	**2d** 99 (>95)	
5	**1e**	Rh[(COD)(*S*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	**2e** 90 (>95)	**3e** 10
6	**1a**	[Rh(COD)(*S*,*S*)-DIOP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP]	**2a** 28 (70)	**3a** 72 (>95)
7[c]	**1a**	[Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+$ClO$_4^-$ and RuBr$_2$[(*R*)-BINAP]	no reaction	

[a] The reaction was carried out using both Rh(I) and Ru(II) catalysts (1 mol % each) at 40 °C for 24 h under 10 atm of hydrogen and additional 24 h under 90 atm of hydrogen. Ethanol was used as a solvent except in entry 2 (MeOH) and entry 3 (*t*-BuOH). [b] The ratio of diastereomers was determined by HPLC. The enantiomeric excesses were determined by ^{1}H NMR analysis using a chral shift reagent Eu[(+)-DPPM] in $CDCl_3$ or by HPLC (CHIRALCEL OD). [c] The phosphine ligand (*R*)-BINAP on the ruthenium catalyst was used instead of (*S*)-isomer.

hydrogenation of **1a** in the presence of both the Rh(I) and the Ru(II) catalysts was examined (step c in Scheme 1).[15] We anticipated that if the Rh(I)- and Ru(II)-catalyzed hydrogenation occurred independently, a one-pot sequential asymmetric hydrogenation of the alkene and ketone moieties in the molecule should be feasible with the coexistence of both catalysts.[16,17] The substrate **1a** and triethylamine (1 equiv) were initially hydrogenated in the presence of both the [Rh(COD)(*S*)-BINAP]$^+$ClO$_4^-$ (1 mol %) and RuBr$_2$[(*S*)-BINAP] (1 mol %) complexes at 40 °C under 10 atm of hydrogen for 24 h. The hydrogen pressure was then increased to 90 atm, and treatment continued for an additional 24 h. These results are depicted in Table 2. The only product observed was **2a** with >95% ee in this one-pot reaction (entry 1). The absolute configuration of this compound is (3*R*,4*R*), and its selectivity was equivalent to that observed in the stepwise operation. It is worth noting that the Rh(I) and Ru(II) catalysts are compatible with high asymmetric induction and that hydrogen pressure can be used to discriminate between the sequential reaction processes. The methyl ester **1b** also underwent the one-pot reaction in methanol solvent providing exclusively **2b** with high enantiomeric excess (entry 2). The *tert*-butyl ester **1c** in *tert*-butyl alcohol did not react (entry 3). Entry 4 shows that the acetamido group can be replaced by a *tert*-butoxycarbonyl group. This one-pot sequential asymmetric hydrogenation should prove effective for the preparation of statine analogues bearing substituted phenyl rings; for example, the 4-chlorophenyl derivatives **2e** and **3e** were prepared from **1e** as a 90:10 ratio of diastereomers, each in enantiomerically pure form (entry 5).

Even more amazing results were observed in the one-pot hydrogenation utilizing Rh(I) and Ru(II) catalysts containing different phosphine ligands. To effect the selective formation of the other diastereomer **3a**, it was deemed essential to choose an alternative phosphine ligand[18] that does not undergo ligand exchange, or minimally, where exchange is significantly slower than the hydrogenation reaction. In fact, when the hydrogenation of **1a** was carried out using [Rh(COD)[(*S*,*S*)-DIOP]$^+$ClO$_4^-$ as the Rh(I) catalyst in the presence of the RuBr$_2$[(*S*)-BINAP] complex, a 72:28 ratio of (3*R*,4*S*)-**3a** and (3*R*,4*R*)-**2a** was obtained in quantitative yield (entry 6 in Table 2). Although the diastereomeric ratio of **3a** to **2a** was less than satisfactory, high enantiomeric excesses of the products were obtained: >95% and 70% ee, respectively. The extent of stereoselectivity for the 4*S* isomer is consistent with that obtained in the stepwise procedure (entry 3 in Table 1).[19] It is conceivable that ligand exchange does not occur under the reaction conditions used in this particular case. On the other hand, when the [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+$ClO$_4^-$ and RuBr$_2$[(*R*)-BINAP] catalysts were used under the same conditions, no reaction was observed (entry 7 in Table 2) although the former catalyst efficiently catalyzes the asymmetric hydrogenation of **1a** by itself (entry 5 in Table 1). These results are reinforced by a ^{31}P NMR study (CD_3OD, 40 °C) in which it was shown that the two signals for [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+$ClO$_4^-$ (doublet at 76.6 ppm, $J_{RhP} = 149$ Hz) and RuBr$_2$[(*R*)-BINAP] (singlet at 32.8 ppm) originally observed, disappeared after 5 min upon mixing under an argon atmosphere, whereas the original signals for [Rh(COD)(*S*,*S*)-DIOP]$^+$ClO$_4^-$ (doublet at 14.7 ppm, $J_{RhP} = 139$ Hz) and RuBr$_2$[(*S*)-BINAP] were unchanged after 6 h under the same conditions.

In summary, we have demonstrated a direct method for the respective preparation of the core units of statine analogues (3*R*,4*R*)-**2**, (3*S*,4*S*)-**2**, (3*R*,4*S*)-**3**, and (3*S*,4*R*)-**3** in enantiomerically pure form. These analogues are prepared from the same molecule **1** in a one-pot, sequential asymmetric hydrogenation process utilizing Rh(I) and Ru(II) catalysts. Further studies aimed at the preparation of statine libraries by this method are underway in our laboratory.

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Supporting Information Available: Synthetic procedures, spectra data, and the determination of absolute configuration (19 pages).

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(15) Attempted sequential hydrogenation using a single catalyst system, either a Rh(I)- or Ru(II)-chiral phosphine complex, was not successful. Rh(I)-catalyzed hydrogenation of ketone moiety in **4a** under higher hydrogen pressure resulted in recovery of **4a**. The one-pot Ru(II)-catalyzed asymmetric hydrogenation of **1a** (RuBr$_2$[(*S*)-BINAP], H_2 90 atm, 60 °C, 24 h) resulted in a 62:38 mixture of **2a** and **3a**, with enantiomeric excesses of 88% and 83% ee, respectively.

(16) No reduction of **1a** by the Ru(II)-catalyst under 10 atm of hydrogen was observed at 40 °C, although the asymmetric hydrogenation of *β*-keto esters using the same catalyst has been reported. See: Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Caño De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675.

(17) One of the reviewers suggested that the addition of triethylamine might slightly inhibit the Ru(II)−BINAP-catalyzed hydrogenation of *β*-keto esters; see: King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689. We thank the reviewer for this suggestion.

(18) The one-pot hydrogenation of **1a** using [Rh(cod)(*R*)-BINAP]$^+$ClO$_4^-$ and RuBr$_2$[(*S*)-BINAP] as catalysts gave a 1:1 mixture of racemic **2a** and **3a**.

(19) Chiral induction for 4*S* and 4*R* was calculated on the basis of the experimental results of the one-pot reaction: 76:24 (52% ee).