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Enantioselective hydrogenation of an α-alkoxy substituted ketone with chiral ruthenium (phosphinoferrocenyl)oxazoline complexes

David M. Tellers,* Matthew Bio, Zhiguo J. Song, J. Christopher McWilliams and Yongkui Sun

Department of Process Research and the Catalysis and Reaction Discovery and Development Lab, Merck and Co., Inc., PO Box 2000, Rahway, NJ 07065-0900, USA

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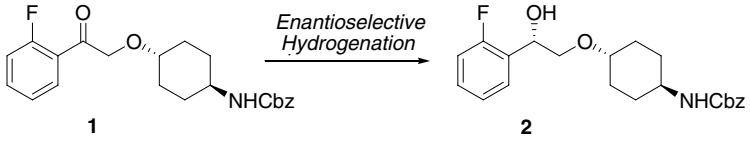
Dedicated to Professor Jack Halpern on occasion of his 80th birthday

Abstract—The discovery and optimization of the highly enantioselective asymmetric hydrogenation of an α-alkoxy substituted ketone is described. The use of a ruthenium (phosphinoferrocenyl)oxazoline catalyst and the appropriate choice of a solvent and a base is the key to the success of this transformation.

1. Introduction

Asymmetric catalytic hydrogenation of prochiral ketones is a useful method for preparing enantioenriched alcohols.[1–3] With that in mind, we envisioned preparing chiral alcohol **2**, a key intermediate en route to a drug development candidate, via asymmetric reduction of the α-alkoxy substituted ketone **1** (Eq. 1).[4,5]



1 **2** (1)

A substantial amount of work has been performed on the asymmetric reduction of α-substituted ketones.[1–3,6] Of these, the majority of examples have focused on α-ester, α-amino, and α-halo ketones.[2,6,7] For α-oxo substituted ketone reductions, of the type shown in Eq. 1, substrate scope has been limited to α-hydroxy, α-phenoxy, and α-methoxy substituted ketones.[2,8–13] In general, the α-hydroxy and α-phenoxy ketone reductions proceeded with higher enantioselectivities than the α-alkoxy substituted ketones. A summary of the catalysts employed in these transformations is presented in Table 1. While potentially applicable to **1**, it is clear from these examples that there is no catalyst system specifically tailored to reduce ketone **1** with high enantioselectivity. As such, we were also interested in expanding the scope of our investigation to include the ruthenium (phosphinoferrocenyl)oxazoline complexes initially described by Sammakia et al. (Fig. 1).[14] Workers at Solvias recently reported that unfunctionalized ketones could be reduced with good enantioselectivities using these catalysts with gaseous hydrogen.[15,16] Herein, we report our hydrogenation screening efforts with the catalysts described above and the discovery that the ruthenium (phosphinoferrocenyl)oxazoline catalysts are active, enantioselective catalysts for the reduction of α-alkoxy substituted ketone **1**. In addition, conditions suitable for the practical scale-up of this reaction are reported.

* Corresponding author. Tel.: +1 732 594 1645; fax: +1 732 594 1499; e-mail: david_tellers@merck.com

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Table 1. Summary of the reported α-oxo substituted ketone reductions[a]

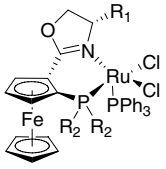
Entry	Chiral catalyst	Substrate (% ee)	Reference
1	(bisphosphine)$RuCl_2$	α-Hydroxyketone (⩽98.5)	2, 3, and 8
2	(xylBinap)(amine)$RuCl_2$	α-Alkoxyketone (37–98), α-phenoxyketone (80)	1 and 12
3[a]	(TsDPEN)Rh(Cp^*)Cl_2	α-Hydroxyketone (94–98), α-tosylketone (93), α-phenoxyketone (88–99)	9 and 13
4[a]	(*cis*-1-aminoindan-2-ol)Ru(*p*-cymene)Cl_2	α-Phenoxyketone (88)	10

[a] Note that entries 3 and 4 employ triethylamine–formic acid as the reducing agent.

2. Results and discussion

2.1. Hydrogenation screen

Ketone **1** was screened against the catalysts highlighted in Table 1 and the chiral ruthenium (phosphinoferrocenyl)oxazoline catalysts (Fig. 1) under the optimal literature conditions.[17] Selected results are presented in Table 2. For the bisphosphine–ruthenium catalysts[18] and the bisphosphine/diamine ruthenium catalysts, low to modest enantioselectivities were observed (Table 2, entries 1–3). We were encouraged by our results with (xyl-Solphos)(*p*-cymene)$RuCl_2$ catalyst (Table 2, entry 1); however, in light of the poor conversion and our results with other catalysts (vide infra), we discontinued this investigation. We then focused our attention on ruthenium and rhodium transfer hydrogenation catalysts and were pleased to find that [(*R*,*R*)-TsDPEN]Ru(*p*-cymene)Cl_2 afforded alcohol **2** in 86% ee.[19] Lower enantioselectivities were obtained with [(−)-*cis*-1-aminoindan-2-ol]Ru(TsDPEN) (5% ee) and [(*R*,*R*-TsDPEN]Rh(*p*-cymene)Cl_2 (64% ee). Finally, the (phosphinoferrocenyl)oxazoline–ruthenium systems were screened against ketone **1**. Each of the ligands showed good enantioselectivities and reactivities in 2-propanol (75–86% ee, 100% conversion) with gaseous hydrogen as the reductant. Enantioselectivities up to 93% were obtained upon switching from 2-propanol to toluene, using aqueous sodium hydroxide to activate the catalyst (Table 1, entries 13 and 14).[20,21] We decided to optimize the hydrogenation with [(*S*,*S*)-N004-2]Ru(PPh_3)Cl_2 as it gave alcohol **2** with higher enantioselectivity than the transfer hydrogenation systems. Furthermore, the use of gaseous hydrogen is advantageous in that rate enhancements are possible by increasing the reaction hydrogen pressure, an option not available with transfer hydrogenations.



[(*S*,*S*)-N00X-2](PPh_3)$RuCl_2$

(*S*,*S*)-N003-2: R_1 = ^{i}Pr, R_2 = Ph
(*S*,*S*)-N004-2: R_1 = ^{t}Bu, R_2 = Ph
(*S*,*S*)-N005-2: R_1 = Ph, R_2 = Ph
(*S*,*S*)-N006-2: R_1 = ^{i}Pr, R_2 = 3,5-Me_2Ph
(*S*,*S*)-N007-2: R_1 = Ph, R_2 = 4-CF_3Ph
(*S*,*S*)-N008-2: R_1 = ^{i}Pr, R_2 = 3,5-Me_2-4-MeOPh

Figure 1. Chiral ruthenium (phosphinoferrocenyl)oxazoline compounds employed in Table 2.

2.2. Reaction optimization with [(*S*,*S*)-N004-2]-Ru(PPh_3)Cl_2

After identifying (*S*,*S*)-N004-2 as a viable ligand lead (Table 2, entry 13), our subsequent development efforts focused on reducing the catalyst loading and improving the volumetric productivity. Ketone **1** was purified by flash chromatography and crystallized from 30% water in methanol, then subjected to a catalyst loading study wherein the concentration of catalyst was decreased

Table 2. Initial catalyst screen for hydrogenation of ketone **1**[a]

Entry	Catalyst	Mol % catalyst[b]	Base	Mol % base[b]	Solvent	% ee[c]
1	[(*R*)-xyl-Solphos]Ru(*p*-cymene)Cl_2[d]	10	NA	NA	MeOH	85
2	(*S*)-(xylBINAP)((*S*)-DAIPEN)$RuCl_2$	0.5	KO^{t}Bu	5	2-Propanol	77
3	(*R*)-(xylphanephos)((*S*,*S*)-DPEN)$RuCl_2$	0.5	KO^{t}Bu	5	2-Propanol	−43
4	[(*R*,*R*)-TsDPEN]Ru(*p*-cymene)Cl_2[e]	6	NA	NA	EtOAc	−86
5	(*cis*-1-aminoindan-2-ol)Ru(*p*-cymene)Cl_2[e]	5	NA	NA	EtOAc	−5
6	[(*R*,*R*)-TsDPEN]Rh(Cp^*)Cl_2[e]	10	NA	NA	EtOAc	−64
7	[(*S*,*S*)-N003-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	78
8	[(*S*,*S*)-N004-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	86
9	[(*S*,*S*)-N005-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	83
10	[(*S*,*S*)-N006-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	75
11	[(*S*,*S*)-N007-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	81
12	[(*S*,*S*)-N008-2](PPh_3)$RuCl_2$[f]	5	KO^{t}Bu	20	2-Propanol	78
13	[(*S*,*S*)-N004-2](PPh_3)$RuCl_2$[f]	5	NaOH (aq)	100	Toluene	93
14	[(*S*,*S*)-N007-2](PPh_3)$RuCl_2$[f]	5	NaOH (aq)	100	Toluene	86

[a] Unless otherwise noted, reaction conditions were as follows: 20 mg **1** per run, [**1**] = 0.05 M, 90 psig, 40 °C, 15 h. >99 HPLC area percent conversion was obtained except for entry 1, where 66 HPLC area percent conversion was obtained.
[b] Relative to ketone **1**.
[c] Determined by chiral supercritical fluid chromatography.
[d] 1000 psig.
[e] Transfer hydrogenation with formic acid/triethylamine (100 mol %).
[f] Prepared from the corresponding ligand and $Ru(PPh_3)_3Cl_2$.

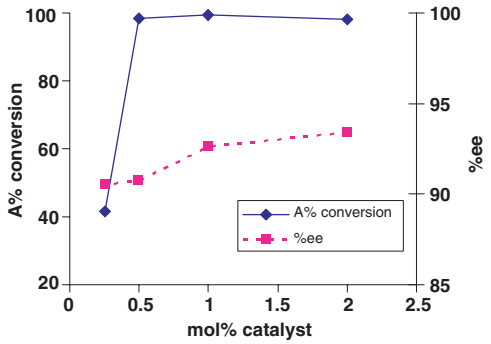


Figure 2. Catalyst loading study for the asymmetric reduction of **1** with (*S*,*S*-N004-2)Ru(PPh_3)Cl_2. Conditions: [**1**] = 0.39 M, 90 psig, 20 h, 40 °C, 100/1 NaOH (aq)/Ru.

from 2 to 0.25 mol % at a constant ketone **1** concentration of 0.39 M (Fig. 2). Complete conversion was obtained at catalyst loadings of 0.5 mol %, with only a minimal decrease in enantioselectivity (~1–2% ee).

While we were satisfied with the results from the catalyst loading study, the reaction was not scaleable because alcohol product **2** forms an insoluble gelatinous mixture under these conditions. We attribute this behavior to the triphasic nature of the reaction mixture (toluene/water/solid product). Although reducing the amount of water in the system by reducing the NaOH loading (75 to 7.5 mol % based on **1**) had little impact on conversion and enantioselectivity, it did not improve the morphology of the end of reaction mixture. The gelling problem was addressed by the addition of polar co-solvents (THF, 2-propanol) to the mixture, resulting in a homogeneous solution phase (Table 3).

Using the appropriate quantity of either THF (50 vol %) or 2-propanol (20–50 vol %) resulted in homogeneous end of reaction solutions with little or no effect on enantioselectivity. The co-solvent 2-propanol was selected for the final optimizations as it offered a wider solubility window than THF. The optimized conditions were performed on a gram scale and the chiral alcohol **2** was obtained in 92% assay yield and 93% ee (Eq. 2). Issues with inhomogeneity were not encountered.

3. Conclusion

In conclusion, we have reported the discovery and development of a highly enantioselective hydrogenation of α-alkoxy ketone **1** using (phosphinoferrocenyl)oxazoline ruthenium catalysts. For ketone **1**, this readily available catalyst system exhibits better enantioselectivity than the current art in ketone reductions (Table 1). The successful extension of this catalyst to other enantioselective ketone reductions should be facilitated by the modular nature of the (phosphinoferrocenyl)oxazoline ligand.

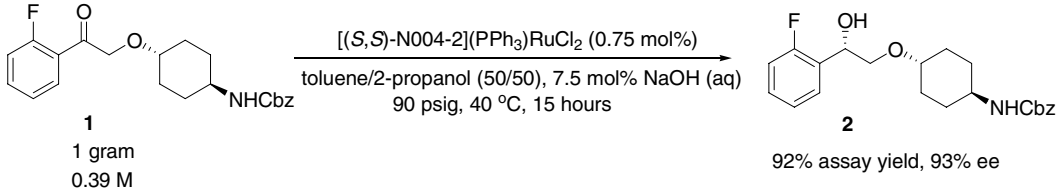
4. Experimental

4.1. Preparation of [(*S*,*S*)-N004-2]Ru(PPh_3)Cl_2

In an inert atmosphere glove box, toluene (0.9 mL) was charged to a vial containing $(PPh_3)_3RuCl_2$ (19 mg, 0.019 mmol) and (*S*,*S*)-N004-2 (9.6 mg, 0.019 mmol). The green solution was stirred until complete dissolution of $(PPh_3)_3RuCl_2$ was observed (~60 min).

4.2. Hydrogenation of ketone 1

In a glove box, a pressure vessel (Fisher-Porter bottle) was charged with **1** (1.0 g, 2.6 mmol), toluene (2 mL), 2-propanol (3 mL), NaOH (39 μL, 0.20 mmol, 5 N), (*S*,*S*-N004-2)Ru$(PPh_3)_2Cl_2$ (0.019 mmol, 0.75 mol %), and a stirbar. The vessel was sealed, removed from the glovebox, and attached to a hydrogen/nitrogen/vacuum



(2)

Table 3. Impact of co-solvents and base loading on the reaction physical properties[a]

Entry	Solvents	Volume ratio	Mol % NaOH (aq)[b]	% ee	End of reaction morphology
1	Toluene/THF	50/50	75	91	Homogeneous
2	Toluene/THF	80/20	75	ND	Gels
3	Toluene/THF	90/10	75	ND	Gels
4	Toluene/IPA	50/50	75	90	Homogeneous
5	Toluene/IPA	80/20	75	ND	Homogeneous
6	Toluene/IPA	90/10	75	ND	Gels
7	Toluene/IPA	50/50	7.5	91	Homogeneous

[a] Conditions: 100 mg **1** per run, [**1**] = 0.39 M, 90 psig H_2, 40 °C, 15 h, 0.75 mol % catalyst. >99 HPLC area percent conversion was obtained for all examples.

[b] Relative to ketone **1**.

manifold. After purging the lines leading up to the pressure vessel (vac/nitrogen × 5), the pressure vessel was purged (nitrogen/vac × 5). The pressure vessel was then purged with hydrogen gas (hydrogen/vac × 3), placed under hydrogen gas (90 psig), and heated to 40 °C. The stirred slurry was left overnight (~15 h), cooled to room temperature and the pressure vessel then vented to atmospheric pressure. The resulting solution was orange and homogeneous. Upon exposure to air, the solution turned green and a black precipitate was observed. Assay yield = 92% (0.92 g); ee = 93%. Enantiomeric excess determined by supercritical fluid chromatography with a Daicel Chemical Industries Chiralpak AD column using 25 mM $^{t}BuNH_2$ in MeOH eluent (1.5 mL/min, 35 °C, 200 psig, 210 nm, rt desired enantiomer = 15.3 min, rt undesired enantiomer = 13.6 min).

4.3. Spectroscopic and analytical data for 1

^{1}H NMR (399.9 MHz, DMSO-d_6, 27 °C) δ 7.82 (dt, $J = 8$ Hz, 2 Hz, 1H), 7.63 (dq, $J = 8$ Hz, 2 Hz, 1H), 7.28 (br m, 6H), 7.13 (d, $J = 8$ Hz, 1H), 4.97 (s, 2H), 4.64 (d, $J = 3$ Hz, 2H), 3.26 (br m, 2H), 1.96 (br d, $J = 10$ Hz, 2H), 1.77 (br d, $J = 10$ Hz, 2H), 1.18 (sextet, $J = 10$ Hz, 4H). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6, 27 °C) δ 196.2 (d, $J = 5$ Hz), 162.8 (s), 160.3 (s), 155.9 (s), 137.8 (s), 135.5 (d, $J = 9$ Hz), 130.5 (d), 128.8 (s), 128.2 (d, $J = 6$ Hz), 126.7 (d, $J = 15$ Hz), 124.0 (d, $J = 23$ Hz), 117.1 (d), 77.6 (s), 73.9 (d, $J = 8$ Hz), 65.6 (s), 49.44 (s), 30.7 (s). HPLC/MS m/z for $[C_{22}H_{24}FNO_4Na]^+$ (M+Na$^+$): calcd 408.15816, obsd 408.15939.

4.4. Spectroscopic and analytical data for 2

^{1}H NMR (399.9 MHz, DMSO-d_6, 27 °C) δ 7.47 (t, $J = 8$ Hz, 1H), 7.26 (br m, 5H), 7.10 (br m, 3H), 5.38 (d, $J = 5$ Hz, 1H), 4.96 (br s, 2H), 4.77 (q, $J = 6$ Hz, 1H), 3.43 (d, $J = 6$ Hz, 2H), 3.20 (br m, 2H), 1.86 (br s, 2H), 1.74 (br s, 2H), 1.15 (br s, 4H). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6, 27 °C) δ 161.0 (s), 158.6 (s), 155.8 (s), 137.8 (s), 130.4 (d, $J = 15$ Hz), 129.3 (d, $J = 9$ Hz), 128.8 (s), 128.7 (d, $J = 4$ Hz), 128.2 (d, $J = 4$ Hz), 124.6 (d, $J = 22$ Hz), 77.3 (s), 72.9 (s), 66.3 (s), 65.6 (s), 49.5 (s), 30.7 (s), 30.6 (s). HPLC/MS m/z for $[C_{22}H_{24}FNO_4Na]^+$ (M+Na$^+$): calcd 410.17381, obsd 410.17462.

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17. It should also be noted that the reduction of ketone **1** with borane–diethylaniline complex in the presence of stoichiometric oxazaborolidine (OAB) alcohol, **2** was obtained in 86% ee. See: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
18. A total of 35 chiral bisphosphine ruthenium catalysts were screened.
19. Various solvents were examined and ethyl acetate was found to give the best enantioselectivity.
20. 5 M NaOH was used.
21. Acceptable reactivity was observed with KO^{t}Bu in toluene; however, significant decomposition was observed. Benzyl alcohol was observed by HPLC suggesting that the CBz group is unstable under these conditions.