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Ru-TsDPEN with Formic Acid/Hünig's Base for Asymmetric Transfer Hydrogenation, a Practical Synthesis of Optically Enriched *N*-Propyl Pantolactam

Ji Zhang,*,† Peter G. Blazecka, Michelle M. Bruendl, and Yun Huang

Research API, Pfizer Global Research & Development, Michigan Laboratories, Pfizer Inc., 2800 Plymouth Road, Ann Arbor, Michigan 48105

ji.zhang@bms.com

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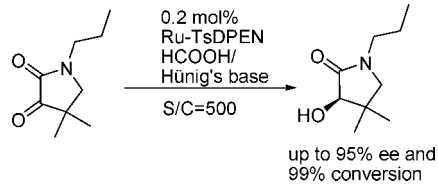

The Noyori−Ikariya catalysts, Ru-TsDPEN **1** or **2**, in combination with HCOOH/Hünig's base (5:2) have been successfully utilized for catalytic asymmetric transfer hydrogenation of α-ketopantolactam, and optically enriched *N*-substituted pantolactam was prepared (S/C = 500, up to 95% ee and 99% conversion in HCOOH/Hünig's base condition). More than 2 kg of this key intermediate **9** has been synthesized efficiently with excellent chemical yield and chiral purity.

Since Noyori and Ikariya[1] first reported that the chiral ruthenium(II) complexes, Ru-TsDPEN **1** and **2** (Figure 1), catalyze the asymmetric reduction of aryl ketones via transfer hydrogenation, in which the simple and practical procedure employs HCOOH/Et_3N (5:2) as the H-donor,[2,3] superior enantioselectivity (up to 99%) and excellent chemical yield have been achieved. When formic acid, a well-behaved, inexpensive, and benign reducing agent, was used, CO_2 was liberated as the side product, making the process proceed irreversibly. The ability of this transformation to provide material with high enantioselectivity while employing a low catalyst loading (S/C up to 5000,)[4] and under safe operating conditions,[5] has subsequently led to the adoption of this elegant method by chemical and pharmaceutical companies.[6] Okano and co-workers at Mitsubishi developed a vastly improved process for the production of (*S*)-1-(3-trifluoromethylphenyl)ethanol, a key intermediate required for the synthesis of a novel fungicide. The robust nature of this practical process was demonstrated through successful pilot plant validation on a 100 kg scale (91% ee, 98% yield).[7] Hansen and co-workers at Merck Laboratories also found that catalytic asymmetric transfer hydrogenation is a scalable and efficient process. Without using air-sensitive chiral catalysts or hazardous reagents, they used (1*S*,2*R*)-*cis*-1-aminoindan-2-ol and dichloro(*p*-cymene)Ru(II) dimmer as the chiral ligand and metal source and 2-propanol as the hydrogen source for catalytic transfer hydrogenation to prepare (*R*)-3,5-bistrifluoromethylphenyl ethanol successfully on a 35 kg scale (91% ee, 87% yield).[8] In recent years, catalytic asymmetric transfer hydrogenation has been widely used for synthesis of chiral alcohols[9] and chiral amines.[10]

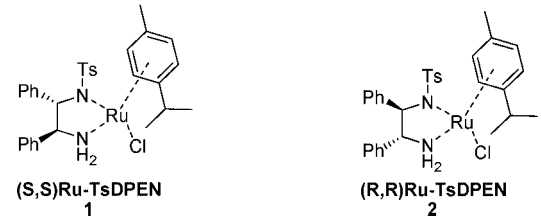

FIGURE 1. Noyori−Ikariya catalysts, Ru-TsDPEN **1** and **2**.

During the course of our development studies, more than 125 g of chirally pure pantolactam **6** (>99% ee) was prepared via racemic intermediate **5**. Since (*R*)-pantolactone **3** is commercially available and inexpensive, our intial strategy utilized an aromatic nucleophilic substitution reaction between (*R*)-pantolactone **3** and aryl fluoride **4** under basic conditions. Although these conditions were found to afford good conversion to **5** (up to 94% yield), the reaction suffered from racemization

* Address correspondence to this author.
† Current address: Process Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543.

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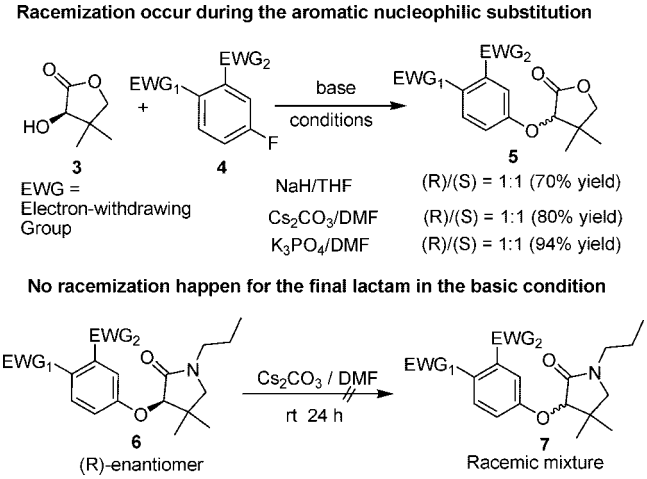
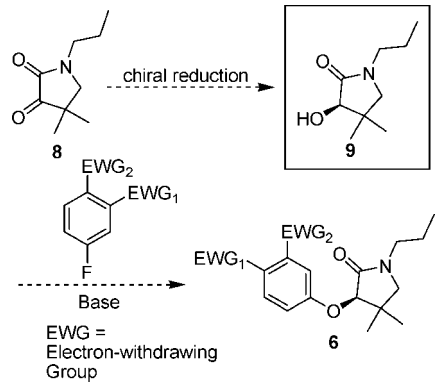
SCHEME 1. Racemization of Intermediate 5 and Stability of Final Product 6 under Basic Conditions



SCHEME 2. Proposed Chiral Approach to Pantolactam 6



of the chiral center to provide racemic product.[11] Although several improvements from the original approach were made (**6** was prepared from racemic **5**, Scheme 1), the downfall of the first generation chemistry is obvious, in that it is a racemic approach, requiring purification by chiral preparative HPLC, which is not practical for the purification of more than a multikilogram of this intermediate since the separation process is tedious and gave 50% undesired (*S*)-enantiomer.

It was hypothesized that the use of an enantiomerically enriched lactam in the coupling reaction would eliminate the observed issues with racemization of the chiral center. A study on the stability of **5** and **6** under basic conditions (NaOH/DMF, K_3PO_4/DMF, and Cs_2CO_3/DMF) confirmed that the chiral γ-lactam **6** is significantly more stable than the γ-lactone **5**, and allowed us to focus on the synthesis of *N*-propylpantolactam **9** (Scheme 2). Herein we would like to report a chiral Ru-TsDPEN/HCOOH/Hünig's base for catalytic asymmetric transfer hydrogenation for the synthesis of (*R*)-*N*-propylpantolactam **9**.

The α-ketopantolactam **8** was readily prepared from dihydro-4,4-dimethyl-2,3-furandione and *n*-propylamine in 71% isolated yield as a white needle solid (Scheme 3).

Initial attempts at asymmetric hydrogenation with commercially available chiral catalysts were somewhat disappointing. Under a variety of conditions the overall conversion and observed enantioselectivity of the transformation was found to be modest.[12] Thus we elected to investigate the use the Noyori catalysts, Ru-TsDPEN **1** and **2**, under transfer hydrogenation conditions (Table 1).[13] The initial result with **1** was encouraging, producing (*S*)-*N*-propylpantolactam **12** as the dominant product in >99% yield (88% ee, Table 1, entry 6).[14]

We next examined different reaction conditions to optimize the enantioselectivity. An examination of the literature revealed that the majority of work in this area has utilized either 2-propanol or the HCOOH/Et_3N (5:2) azeotropic mixture as both the hydrogen donor and solvent, in combination with the ruthenium catalyst. It was to our surprise that other amines, especially tertiary amine bases, have limited use for this transformation since the initial report by Leitner and Brunner in 1988 on the use of HCOOH/Et_3N (5:2) as the hydrogen source.[15] During their study on the transfer hydrogenation of itaconic acid, Brunner and Leitner also found the use of optically

SCHEME 3. Synthesis of Ketopantolactam from α-Ketopantolactone 8

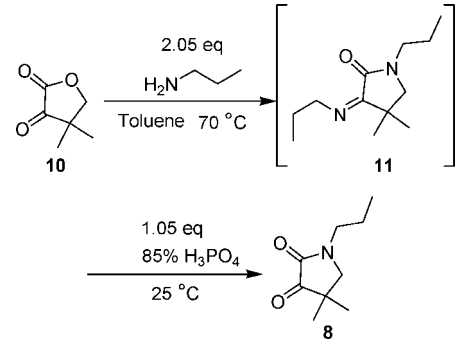
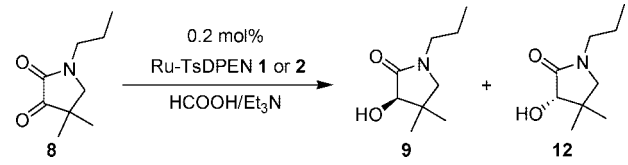


TABLE 1. Asymmetric Transfer Hydrogenation Using RuTsDPEN 1 or 2 with HCOOH/Et_3N[a]



entry	time/temp	catalyst	% ee	% conversion (conf)
1	1 h/35 °C	**2**	88	94 (*R*)
2	2 h/35 °C	**2**	88	99 (*R*)
3	3 h/35 °C	**2**	88	99 (*R*)
4	4 h/35 °C	**2**	88	99 (*R*)
5	+15 h/25 °C	**2**	88	>99 (*R*)
6	4 h/50 °C	**1**	88	>99 (*S*)

[a] Yield and ee were determined by chiral GC analysis, using chiral column: Supelco Beta Dex-120, 30 m, 0.25 mm i.d., 0.25 μm film. Scale: 4.5 g of **8** (26.6 mmol). S/C = 500.

(11) The problem of racemization could be overcome via use of $Ca(OH)_2$/DMF, which eliminated epimerization; however, the conversion was low at room temperature. Heating the reaction to 40 °C increased the yield to 52%, but the ratio of *R*/*S* dropped to 85/15 from 95/5.

(12) Enantioselective hydrogenation of ketopantolactone was achieved with a Pt catalyst modified by cinchonidine at high pressure (69−70 atm), giving the *R*-pantolactone **3** with 92% ee. See: (a) Schürch, M.; Künzle, N.; Mallat, T.; Baiker, A. *J. Catal.* **1998**, *176*, 569. (b) Künzle, N.; Szabo, A.; Schürch, M.; Wang, G.; Mallat, T.; Baiker, A. *Chem. Commun.* **1998**, 1377.

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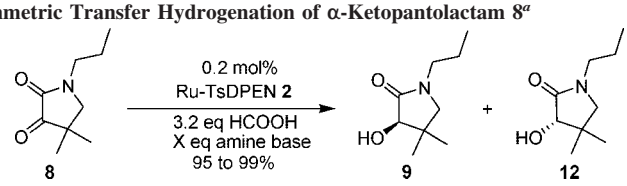
(14) Configurations of **9** and **12** were confirmed and assigned based on the configuration of final compound **6** (manuscript in preparation).

TABLE 2. Optimization of the Asymmetric Transfer Hydrogenation of α-Ketopantolactam 8[a]



entry	time/temp	HCOOH:amine base	cat. (mol %)	% ee
1	4 h/50 °C	HCOOH:Et_3N (1:1)	0.2	89
2	24 h/25 °C	HCOOH:Et_3N (1:1)	0.2	93
3	5 h/35 °C	HCOOH:Et_3N (1:1)	0.2	89
4	24 h/25 °C	HCOOH:Et_3N (5:2)	0.2	91
5	24 h/25 °C	HCOOH:*N*-methyldicyclohexylamine (5:2)	0.2	88
6	24 h/25 °C	HCOOH:*N*-methylmorpholine (1.2:1)	0.2	81
7	24 h/25 °C	HCOOH: N,N-dimethylaminoethanol (1.2:1)	0.2	92
8	24 h/25 °C	HCOOH:*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.2:1)	0.2	89
9	24 h/25 °C	HCOOH:(−)-Sparteine (5:2)	0.2	95
10	24 h/25 °C	HCOOH:Hünig's (5:2)	0.2	95
11	Cp*IrCl-TsDPEN 2 h/50 °C	HCOOH:Et_3N (1:1)	0.2	86
12	Cp*RhCl-TsDPEN 24 h/25 °C	HCOOH:Et_3N (1:1)	0.2	68

[a] Yield and ee were determined by chiral GC analysis, using chiral column: Supelco Beta Dex-120, 30 m, 0.25 mm i.d., 0.25 μm film. Scale: 4.5 g of **8** (26.6 mmol) to 90 g of **8** (530 mmol). S/C = 500.

active phenethylamine instead of triethylamine increases the enantioselectivity to >97% ee[16] and that the use of HCOOH/chiral amine is slightly better than the use of HCOOH/Et_3N for the enantioselectivity. Therefore, we elected to conduct a screening of various tertiary amine bases in combination with formic acid as well as alternative catalyst systems for the asymmetric transfer hydrogenation of **8**.

There have been few detailed studies investigating the effect of either the ratio of formic acid to triethylamine or the solvent on the asymmetric transfer hydrogenation reaction.[17] The elegant work conducted by Okano and co-workers[7] found among several different combinations of HCOOH/Et_3N that the reaction rate of asymmetric transfer hydrogenation was fastest when the molar ratio of formic acid to triethylamine was unity. Although an equimolar mixture of formic acid and triethylamine was immiscible, the addition of ketone made the mixture homogeneous. Our study (Table 2, entries 1, 2, and 3) also confirmed that using HCOOH/Et_3N (1:1) is ideal to achieve high chemical yield (>99%) with excellent enantioselectivity (up to 93% ee). From the study (Table 2), it is clear that Hünig's base is superior to Et_3N (entries 4 and 10) and provides comparable results to that of the chiral amine (−)-sparteine (entries 9 and 10). Additional screening of alternative catalyst systems found that optimal results are obtained with ruthenium-based systems (entries 11 and 12). The optimized reaction conditions were successfully implemented (entry 10) on inputs of 18 and 90 g of **8** to provide (*R*)-*N*-propylpantolactam **9** in 99% yield with enantioselectivities of 94% and 92%, respectively.

There has been one report that utilized B-chlorodiisopinocampheylborane (DIP-Chloride) for the enantioselective reduction of a ketopantolactam, affording product with a chiral purity of 88% ee for the *R* isomer and 64% ee for the *S* isomer.[18] Although there are several reports describing the use of chiral Rh(I),[19] Ru(II),[20] and Pt/Al_2O_3[21] for asymmetric hydrogenation of ketopantolactone and α-ketoesters,[22] to the best of our knowledge this is the first example of a catalytic asymmetric transfer hydrogenation for chiral reduction of a ketopantolactam, providing the product with excellent enantioselectivity.

The γ-lactams have proven to be valuable intermediates for the synthesis of γ-aminobutyric acid (GABA), such as pregabalin (Lyrica),[23] and α-hydroxy acids have been clearly demonstrated useful with biological importance.[24] Moreover, recent studies confirmed that α-hydroxy-γ-aminobutyric acids exist and play an important role in some biologically and pharmaceutically relevant molecules, such as Butirosin.[25] We believe that our practical method for the generation of optically enriched pantolactam will create a new way to access structurally complex and enantiomerically pure α-hydroxy-γ-amino acids[26] and α-hydroxy γ-lactams.[27]

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In summary, we have developed a simple, efficient, and highly enantioselective method for the preparation of optically enriched *N*-propylpantolactam. The ability to utilize the chiral Ru(II) complex Ru-TsDPEN in combination with hydrogen sources such as formic acid and amine bases such as Hünig's base and (−)-Sparteine for the asymmetric transfer hydrogenation of an α-ketopantolactam represents an imporantant advance of this reaction. Besides the widely used HCOOH/Et_3N system, the combination of HCOOH/Hünig's base turns out to be an excellent H-donor for the asymmetric transfer hydrogenation, providing an alternative for optimizing the enantioselectivity. The α-ketopantolactam **8** was efficiently reduced to optically enriched *N*-propylpantolactam **9** (S/C = 500, up to 95% ee and up to 99% conversion). More than 2 kg of this key intermediate **9** was prepared with excellent chemical yield and chiral purity, which in turn facilitated the successful synthesis of compound **6** on a multikilogram scale.

Expertmental Section

1-(Propyl)-4,4-dimethyl-2,3-pyrrolidione, 8. To a solution of dihydro-4,4-dimethyl-2,3-furandione (256.3 g, 2.0 mol) in toluene (1025 mL) at 0 °C was added *n*-propylamine (242.4 g, 4.10 mol) dropwise while maintaining the temperature below 10 °C. The reaction mixture was heated to 70−75 °C for 20 h. After the reaction mixture was cooled to rt then charged with toluene (770 mL), it was cooled to 5−10 °C. Next 85 wt % of phosphoric acid (242.1 g, 2.10 mol) was added over 30 min while maintaining the temperature below 10 °C. Then the reaction mixture was warned to 20−25 °C and maintained at this temperature for 4−5 h. The reaction mixture was filtered through a silica gel pad and rinsed with EtOAc (3 × 510 mL) and the resulting contents were concentrated under reduced pressure until ∼400 mL remained in the reaction vessel. Heptane (2400 mL) was then added slowly over 20 min while maintaining the temperature between 45 and 55 °C. The mixture was then cooled to rt over 1.5 h and then to 0−5 °C for 2 h. The contents of the reaction vessel were filtered and the filter cake was washed with heptane (400 mL) to yield 240 g (1.42 mol) of white solid (yield: 71%, purity >99%, checked by GC). ^{1}H NMR (400 MHZ, $CDCl_3$, ppm) δ 0.62 (3H, t, J = 7.4 Hz), 0.93 (6H, s), 1.36 (2H, m, J = 7.4 Hz), 3.16 (4H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 11.2, 20.0, 23.6, 39.9, 45.9, 55.8, 159.3, 204.5. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88, H, 8.93, N, 8.28. Found: C, 63.89, H, 8.74, N, 8.31.

***R*-(Propyl)-3-hydroxy-4,4-dimethylpyrrolidin-2-one, 9.** To a solution of *N*,*N*-diisopropylethylamine (90. 0 g, 0.70 mol) at −10 °C was added formic acid (80.4 g, 1.75 mol) dropwise while maintaining the temperature below −5 to 10 °C. After the addition was completed, a solution of Noyori−Ikariya catalyst, (*R*,*R*)Ru-TsDPEN **2** (0.68 g, 1.06×10^{-3} mol, dissolved in 15 mL of anhydrous DMF), was added, followed by addition of 1-(propyl)-4,4-dimethyl-2,3-pyrrolidione (90.0 g, 0.53 mol). The reaction mixture was warned to 20 to 25 °C slowly, then stirred at this temperature for 20 to 24 h. The reaction mixture was then assayed (by GC and chiral GC) to contain 90.2 g of product (92% ee, >99% yield).

(±)1-(Propyl)-3-hydroxy-4,4-dimethylpyrrolidin-2-one. This compound was prepared by reduction of 1-(propyl)-4,4-dimethyl-2,3-pyrrolidione by $NaBH_4$ as a white solid. ^{1}H NMR (400 MHZ, CD_3OD, ppm) δ 0.88 (3H, t, J = 7.4 Hz), 0.97 (3H, s), 1.16 (3H, s), 1.53 (2H, sextet, J = 7.5 Hz), 3.04 (1H, d, J = 9.9 Hz), 3.11 (1H, d, J = 9.9 Hz), 3.20 (2H, t, J = 7.4 Hz), 3.90 (1H, s), 4.80 (1H, s). ^{13}C NMR (100 MHz, CD_3OD, ppm) δ 10.5, 19.6, 20.2, 23.8, 38.5, 44.3, 56.6, 78.0, 175.0. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13, H, 10.01, N, 8.18. Found: C, 63.55, H, 10.11, N, 7.91.

Supporting Information Available: Experimental procedures, spectral and analytical data for all products, and additional structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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