Asymmetric Reductive Amination

Highly Enantioselective Hydrogen-Transfer Reductive Amination: Catalytic Asymmetric Synthesis of Primary Amines**

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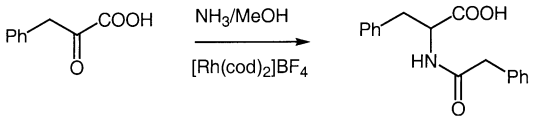
Optically active amines are attracting increasing interest in the food, agrochemical, and pharmaceutical industries as building blocks for novel compounds and as templates for asymmetric synthesis. One of the most common methods for preparing amines is the reductive amination of carbonyl compounds.[1] We have successfully explored the rhodium-catalyzed asymmetric reductive amination with hydrogen as the reducing agent.[2] Recently, we developed a highly active and enantioselective catalytic system for the reductive amination of α-keto acids.[3] In the course of our studies we observed that the reaction of phenylpyruvic acid in methanolic ammonia at 60 °C in the presence of a Rh catalyst smoothly furnished *N*-(phenylacetyl)phenylalaninamide [Eq. (1)]. The formation of this product from phenylpyruvic acid and ammonium sulfate proceeds in the absence of a catalyst at a higher temperature (105 °C).[4]



(1)

This observation prompted us to investigate a reductive amination mediated by chiral catalysts under hydrogen-transfer conditions. The reduction of carbonyl compounds to amines with formic acid or formamide is known as the Leuckart–Wallach reaction.[5] Few studies on the use of catalysts in this reaction have been reported in the literature.[6] As part of our ongoing research into the asymmetric hydrogen-transfer reductive amination,[7] we report herein our results from the screening of a variety of catalyst types and describe an effective catalytic system for the production of simple amines with high enantioselectivity.

Two conventional hydrogen sources, isopropyl alcohol and formic acid,[8] were considered. In the reductive amination of acetophenone with ammonia in isopropyl alcohol only $[Rh(C_5Me_5)Cl_2]_2$ demonstrated acceptable activity. In the presence of this catalyst, 1-phenylethylamine (**1**) and 1-phenylethanol (**2**) were produced in 12 h at 70 °C in yields of 30 % and 1 %, respectively. Figure 1 shows the yields determined by GC of **1** and **2** and the enantiomeric excess of **1** in the reaction of acetophenone with ammonium formate for the different Rh, Ir, and Ru complexes that were tested as catalysts. The use of Rh and Ir complexes resulted in poor enantioselectivities under all conditions investigated. Therefore, we concentrated on Ru systems with ammonium formate as the hydrogen donor (Leuckart–Wallach-type reductive amination).

As can be seen in Figure 1, the best enantioselectivities were observed with Ru catalysts with a binap or a tol-binap ligand. The degree of asymmetric induction by both catalysts was evaluated for a number of aryl ketones. The reactions were quenched after 24 h, and the crude reaction mixtures were analyzed directly by HPLC for the *ee* values of the products. The results indicate that the Ru–tol-binap complex gives higher enantioselectivities than the Ru–binap complex (Table 1). As a result of the very broad peaks observed with our fast method of HPLC analysis, we were unable to detect another enantiomer in the reactions represented in entries 2, 3, and 5 of Table 1.

Optimization of the reaction conditions by screening additives was performed with acetophenone in the presence of [((*R*)-tol-binap)$RuCl_2$] (Table 2). Acids were found to accelerate the reaction but to lower the asymmetric induction. The addition of ammonia led to enhancement of the enantioselectivity but a decrease in the reactivity. However, aqueous ammonia was found to increase the yield of the alcohol. The best enantioselectivities were generally observed when 5 to 10 equivalents of $HCOONH_4$ in NH_3/methanol (15–25 %) and temperatures between 60 and 85 °C were used.

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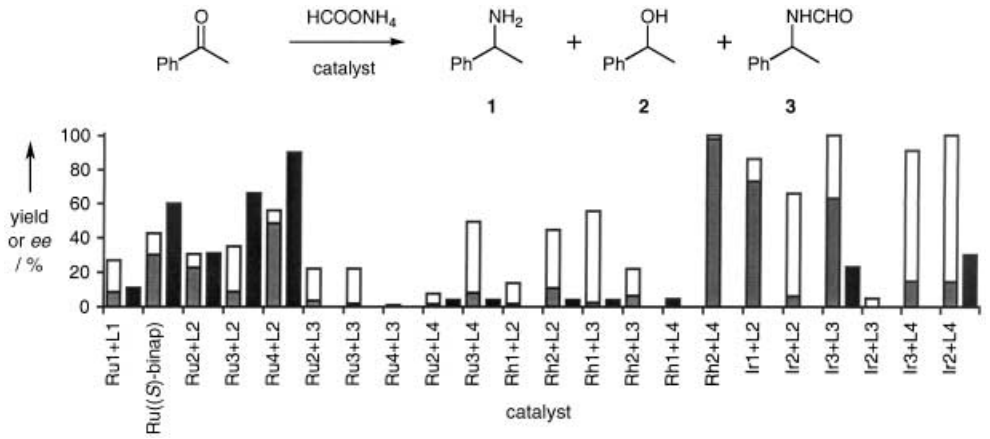

Figure 1. The yields of **1** (shadowed bars) and **2** (white bars), as determined by GC analysis, and the enantiomeric excess of **1** (black bars) after 24 h in the reductive amination of acetophenone (0.5 mmol) with ammonium formate in ammonia solution (15–25%, 1 mL) in methanol at 70°C in the presence of the catalyst indicated (0.5 μmol): Ru1 = $[Ru(DMSO)_4Cl_2]$; Ru2 = $[Ru(cymene)_4Cl_2]_2/2$; Ru3 = $[Ru(PPh_3)_3Cl_2]$; Ru4 = $[Ru(C_4H_7)_2$-(cod)]; Rh1 = $[Rh(cod)_2]OTf$; Rh2 = $[Rh(C_5Me_5)Cl_2]_2/2$; Ir1 = $[Ir(cod)Cl]_2/2$; Ir2 = $[Ir(C_5Me_5)Cl_2]_2/2$; Ir3 = $[Ir(C_8H_{14})_2Cl]_2/2$; L1 = (1*R*,2*R*)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphanylbenzoyl); L2 = (*R*)-2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl; L3 = (2*R*,3*R*)-2,3-bis(diphenylphosphanyl)bicyclo[2.2.1]hept-5-ene; L4 = (1*R*,2*R*)-1,2-diphenyl-1,2-ethylenediamine. DMSO = dimethyl sulfoxide; cod = cyclooctadiene; Tf = trifluoromethanesulfonate.

Table 1: Enantioselectivities in the Leuckart–Wallach-type reductive amination of ketones.[a]

Entry	Ketone	*ee* [%][b]	
		Catalyst A[c]	Catalyst B[d]
1	acetophenone	83 (*S*)	91 (*R*)
2	4′-methylacetophenone	10 (*R*)	>95 (*R*)
3	4′-methoxyacetophenone	6 (*R*)	>95 (*R*)
4	4′-bromoacetophenone	60 (*S*)	84 (*R*)
5	2-acetylnaphthalene	90 (*S*)	>95 (*R*)

[a] Ketone (0.5 mmol), ammonium formate (1 mmol), catalyst (5 μmol), NH_3/MeOH (15–20%, 1 mL), 24 h, 70°C. [b] The *ee* values were determined by HPLC analysis. [c] [((*S*)-binap)$RuCl_2$]. [d] [((*R*)-tol-binap)-$RuCl_2$].

Table 2: Effect of additives in the enantioselective Leuckart–Wallach-type reductive amination of acetophenone with [((*R*)-tol-binap)$RuCl_2$] as the catalyst.[a]

Entry	Additive	Yield [%]			*ee* of **1** [%]
		1	**2**	**3**	
1	–	37.3	2.9	48.0	85
2	NH_3[b]	15.0	2.0	17.2	90
3	NH_4OH/H_20[c]	13.6	14.4	3.4	92
4	TsOH[d]	57.5	13.1	20.8	69
5	HCl[d]	78.9	10.8	10.3	60
6	HBF_4[d]	69.7	13.7	12.1	20

[a] Acetophenone (0.5 mmol), ammonium formate (2.5 mmol), [((*R*)-tol-binap)$RuCl_2$] (10 μmol), MeOH (1 mL), 10 h, 60°C. The product ratio was determined by GC analysis. [b] NH_3/MeOH (20%); [c] Aqueous ammonia (25%, 0.5 mL). [d] Additive: 0.5 mmol.

A series of ketones were examined under the optimized conditions (Table 3). The desired products were formed as the free amines and in their *N*-formylated form. The *N*-formyl derivatives are the main products in the Leuckart–Wallach reductive amination of aromatic ketones.[5b] The amines were obtained in good yields with moderate to high enantioselectivities (86–98% *ee*) after hydrolysis when aromatic ketones were used as substrates. The best asymmetric induction was observed in the reaction of 4′-nitroacetophenone at 60°C (98% *ee*).

In the reaction of 2-octanone under the standard conditions, full consumption of the starting material occurred within 24 h, but only a

Table 3: Enantioselective Leuckart–Wallach-type reductive amination of ketones with [((*R*)-tol-binap)-$RuCl_2$] as the catalyst.[a]

Entry	Substrate	*t* [h]	Ketone [%]	Amine [%]	Formyl amine [%]	Alcohol [%]	Yield[d] [%]	ee[e] [%]
1	acetophenone	20	5	75	19	1	92	95
2	propiophenone	21	0	22	78	0	89	95
3	3′-methylacetophenone	24	23	38	39	0	74	89
4	4′-methylacetophenone	21	0	8	91	0	93	93
5	4′-methoxyacetophenone	24	3	64	32	1	83	95
6	4′-chloroacetophenone	24	0	6	94	0	93	92
7	4′-bromoacetophenone	48	0	10	90	0	56	91
8	4′-nitroacetophenone	48	0	45	55	0	92	95[f]
9	1-acetylnaphthalene	30	14	11	69	6	69	86
10	2-acetylnaphthalene	30	0	18	82	0	91	95
11	2-octanone[b]	17	0	36	64	0	44	24 (*S*)
12	2-methylcyclohexanone[b,c]	20	0	(33:22)	(32:13)	0	63 (64:36)	17:64[g]

[a] For the reaction conditions, see Experimental Section: substrate (5 mmol), ammonium formate (50 mmol), [((*R*)-tol-binap)$RuCl_2$] (1 mol%), 85°C, NH_3/MeOH (15–20%, 20 mL). The product ratio was determined by GC analysis. [b] In MeOH (20 mL), without ammonia. [c] *Cis/trans* ratios are given in brackets. [d] Yield of the isolated amine after hydrolysis. [e] Products have the *R* configuration, with the exception of the last two entries. [f] When the reaction was carried out at 60°C, 98% *ee* was observed. [g] *Cis* isomer: 17% *ee*, *trans* isomer: 64% *ee*.

trace amount of 2-octylamine was detected. However, a 44% yield of the desired product was isolated with 24% *ee* in the absence of ammonia as additive (Table 3, entry 11). The reductive amination of 2-methylcyclohexanone proceeded well under both sets of conditions. Although the *cis*/*trans* stereoselectivity was not affected by the inclusion of ammonia as an additive, inferior enantioselectivities were observed. Thus, the *cis* isomer was obtained in 9% *ee* and the *trans* isomer in 43% *ee* under the standard reaction conditions, whereas in the absence of ammonia 17% *ee* was observed for the *cis* isomer and 64% *ee* for the *trans* isomer (Table 3, entry 12). Interestingly, a nearly identical *cis*/*trans* ratio of 3:2 was reported for the corresponding Leuckart–Wallach reaction.[9]

In summary, we have developed a new and efficient method for the synthesis of primary amines from ketones in an asymmetric catalytic manner. This method displays a high level of asymmetric induction for aromatic ketones. Ammonia is a crucial parameter in the catalytic system described, in terms of the enantioselectivities observed.

Experimental Section

[((*R*)-tol-binap)$RuCl_2(DMF)_x$][10] (50 mg, ca. 50 μmol; DMF = dimethylformamide), the ketone (5 mmol), and ammonium formate (3.16 g, 50 mmol) were placed in a 35-mL Ace pressure tube (Aldrich) under argon. Freshly condensed ammonia in dry methanol (20–25%, 20 mL) was added, then the tubes were sealed under argon and stirred at 85 °C for the time indicated. Following evaporation of the volatile components, the residue was dissolved in ethanol (10 mL), and hydrochloric acid (6N, 5 mL) was added. The mixture was then heated at reflux for 1 h to hydrolyze the formyl derivatives, then cooled, diluted with water (10 mL), and extracted with ether to remove any unreacted ketone. The aqueous layer was made alkaline by the addition of ammonia solution (25%, 4 mL), then extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to afford the crude amine, which was shown to be pure by ^1H NMR spectroscopy. The optical purity was determined by GC analysis of the corresponding acetamide on a chiral phase (Chrompack, CP Chirasil-DEX CB), as reported previously.[11]

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