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Practical Synthesis of (*S*)-1-(3-Trifluoromethylphenyl)ethanol via Ruthenium(II)-catalyzed Asymmetric Transfer Hydrogenation

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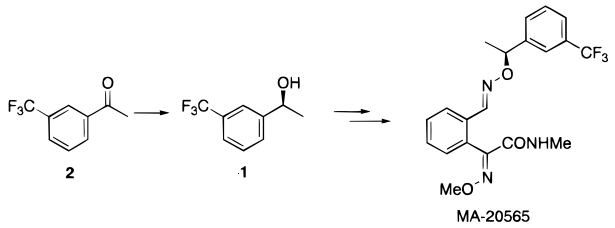
Abstract:

(*S*)-1-(3-Trifluoromethylphenyl)ethanol which is useful as an agrochemical intermediate was prepared from the corresponding acetophenone by asymmetric transfer hydrogenation. Removal of acetone raised the yield and maintained the optical purity when *i*-PrOH was used as the hydrogen source; however, this operation was not practical at industrial scale. Then formic acid was examined as the hydrogen source, and dramatic acceleration of the reaction rate was achieved by optimization of the reaction conditions to establish asymmetric transfer hydrogenation at industrial scale.

Introduction

Optically active 1-(phenyl)ethanol is widely used in the pharmaceutical, agrochemical, and aromachemical areas. Recently, Mitsubishi Chemical reported the synthesis of a wide-spectrum agricultural fungicide, (*S*)-MA20565, from (*S*)-1-(3-trifluoromethylphenyl)ethanol, **1**.[1] **1** has previously been prepared by optical resolution,[2a] selective acylation by a lipase,[2b] asymmetric hydrosilylation of styrene[2c] and chiral oxazaborolidine reduction of acetophenone.[2d] In these processes, the reduction of the ketone was selected due to the availability of *m*-trifluoromethylacetophenone **2** and the practical features of the reaction.[3] Recently, many enantioselective reductions of acetophenone derivatives have been reported.[4] We selected Noyori's Ru(II)-catalyzed asymmetric transfer hydrogenation (ATH) because of the high ee, low catalyst cost, and safe operation (Scheme 1).[5]

Scheme 1



Results and Discussion

Reduction by *sec*-Alcohol. Secondary alcohols were initially examined as the hydrogen source. The catalyst was prepared in situ by heating a mixture of $[RuCl_2(arene)]_2$ and (1*S*,2*S*)-*N*-(arylsulfonyl)-1,2-diphenylethylenediamine. To a mixture of the ruthenium catalyst, an alcohol, KOH, and ketone **2** were added, and the mixture was then stirred. $[RuCl_2(benzene)]_2$ showed a rather high yield but lower ee than $[RuCl_2(p\text{-cymene})]_2$. As the hydrogen source, 2-butanol was found not to be suitable on the basis of both the yield and ee, and ethanol showed a reaction inhibition estimated by the acetaldehyde formation. An arylsulfonyl group on the nitrogen of the ligand was examined and *p*-methoxysulfonyl showed the best result (Table 1). The equilibrium conversion of **2** was higher than acetophenone and reached 96% at 1 M concentration. The high conversion is due to the substituent effect of *m*-CF_3 because a lower reaction rate was found for the Pd-catalyzed hydrogenolysis when **1** was used as the hydrogen source.[6] The ee was lower than that of acetophenone and declined during the reaction and gave the (*S*)-alcohol **1** with 89% ee.

Further optimization was performed using the readily available $[RuCl_2(p\text{-cymene})]_2$ and (*S*,*S*)-*N*-*p*-tosyl-1,2-diphenylethylene-1,2-diamine ligand ((*S*,*S*)-TsDPEN) (Table 2). Although both an increase in catalyst and low reaction concentration were effective, they are not practical at a large scale. Noyori described that the reverse reaction with acetone caused a fall in the ee. The removal of acetone at reduced pressure, maintained the initial optical purity and raised the conversion at the 50 g scale.[7] However, the acetone removal process was predicted to be problematic scale-up.

Reduction by Formic acid. Next, the use of formic acid as a hydrogen source was investigated. For this reaction, we

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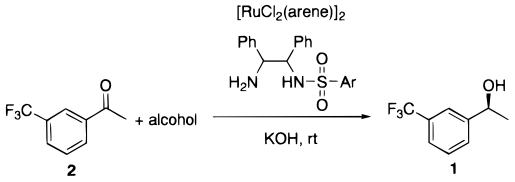
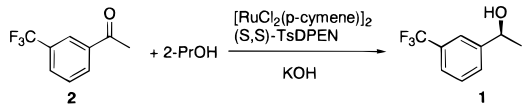
Table 1. **Asymmetric Transfer Hydrogenation of 2 in sec-alcohol[a]**



entry	alcohol[b]	arene	Ar	*S/C*	time, h	yield[c], %	ee[c], %
1	2-PrOH	*p*-cymene	*p*-tolyl	1000	6	86	89
2	2-BuOH	*p*-cymene	*p*-tolyl	200	7	46	83
3	2-PrOH	benzene	*p*-tolyl	200	3	96	86
4	2-PrOH	*p*-cymene	*p*-chlorophenyl	1000	6	95	86
5	2-PrOH	*p*-cymene	p-methoxyphenyl	1000	6	96	89
6	2-PrOH	*p*-cymene	mesityl	1000	4	14	79
7	2-PrOH	*p*-cymene	2,4,6-triisopropylphenyl	1000	4	15	68

[a] Ru:(S,S)-TsDPEN:KOH = 1:2.5. [b] 1 mol concentration of **2**. [c] Yield and ee were determined by HPLC analysis using a Daicel Chiralcel OJ column.

Table 2. **Asymmetric Transfer Hydrogenation of 2 in 2-propanol[a]**

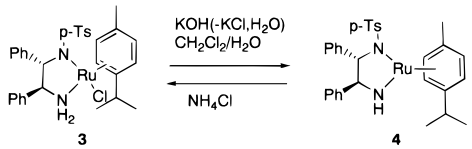


entry	*S/C*	conc.[b], M	temp, °C	time, h	yield[c], %	ee[c], %
1	1000	1	rt	6	86	89
2	200	1	rt	5	94	88
3	200	0.1	rt	5	97	91
4	500	0.66	26	5	99	88

[a] Ru:(S,S)-TsDPEN:KOH = 1:2.5. [b] Mol concentration of **2**. [c] Yield and ee were determined by HPLC analysis using a Daicel Chiralcel OJ column. [d] The reaction was carried out at 45−55 mmHg, and acetone was removed.

used the chiral Ru complex ((*S*,*S*)-TsDPEN−Ru, **3**, prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ and (*S*,*S*)-TsDPEN.[5f] In the field of transfer hydrogenation the azeotropic mixture of formic acid and triethylamine (molar ratio 5:2) has been used as a hydrogen source, where for example Noyori has reported an excellent asymmetric transfer hydrogenation using the ruthenium complex **3** and the hydrogen donor (Scheme 2).[5d]

Scheme 2



Although the use of formic acid was attractive with respect to the high conversion and selectivity, a slow reaction rate was the problem. We followed the course of alcohol formation and found an induction period prior to acceleration of the reaction. Although an aprotic polar solvent was effective in accelerating the reaction, the induction period remained (Figure 1). The active 16-electron species **4** reported by Noyori gave the same results. This suggests that acceleration in the middle stage of the reaction was caused by the consumption of excess formic acid. We examined the ratio between formic acid and triethylamine, and found

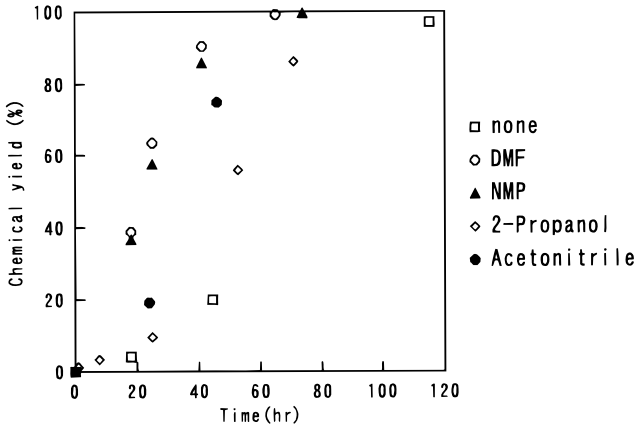


Figure 1. **Effect of solvent. Reaction conditions: substrate: formic acid: triethylamine:Ru = 1:5:2:0.02; solvent:formic acid−triethylamine mixture = 1:2 (v:v); temp, rt.**

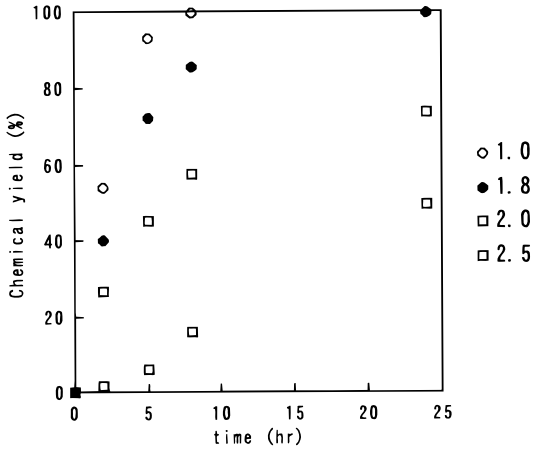


Figure 2. **Effect of the ratio of formic acid to triethylamine. Reaction conditions: substrate:formic acid:Ru = 1:5:0.02; temp, rt.**

that the reaction was fastest when the molar ratio of formic acid to triethylamine was 1 (Figures 2 and 3). Though an equimolar mixture of formic acid and triethylamine was immiscible, the addition of substrate **2** made the mixture homogeneous. The use of an equimolar mixture of formic acid and triethylamine in slight excess relative to substrate

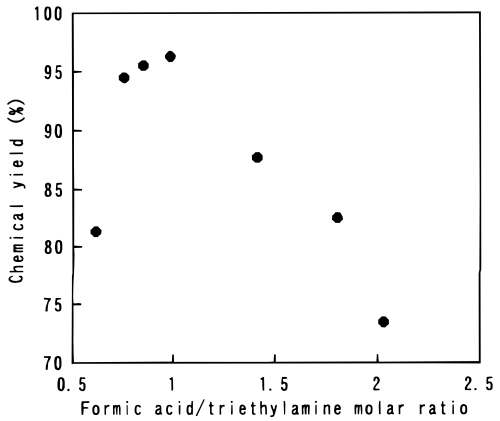
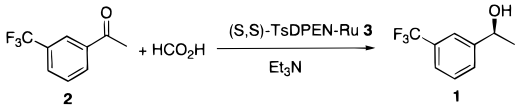


Figure 3. **Effect of the ratio of formic acid to triethylamine. Reaction conditions: substrate:formic acid:Ru = 1:1.16:0.005; temp, 50 °C; time, 5 h.**

Table 3. **Asymmetric Transfer Hydrogenation of 2 with HCO_2H**



entry	*S/C*	HCO_2H (equiv)	Et_3N (equiv)	temp, °C	time, h	yield[a], %	ee[a], %
1[b]	500	11.5	4.6	rt	77	95	95
2[b]	1000	11.5	4.6	60	8	93	90
3[c]	1000	1.05	1.05	30	24	99	93
4[c]	5000	1.05	1.05	50	30	96	91

[a] Yield and ee were determined by GC analysis using a Chrompak Cyclodextrin-B-236M-19 0.25 mm, 50 m. [b] HCO_2H and Et_3N were used as a 5:2 azeotrope mixture. [c] HCO_2H and Et_3N were used as a mixture by simple mixing.

was sufficient to enable completing of the reaction using a *S/C* = 5000 (Table 3.). After the reaction stopped, fractional distillation gave pure **1.** The triethylamine can be recycled of industrial scale. The Ru catalyst in the distillation residue had a rather low activity compared to that of the freshly prepared complex.

CO_2 is evolved as a by-product during this reaction, and we found that disengagement of CO_2 from the reaction mixture was important for the rate of reaction. The reaction was faster when scaled up (100 kg of **2**, Figure 4), probably due to effective release of CO_2 from the reaction being regulated with good agitation of large-scale provided by an impeller.

Conclusions

We have developed a vastly improved process for the production of (*S*)-1-(3-trifluoromethylphenyl)ethanol, **1,** a key intermediate required for the synthesis of the new fungicide, (*S*)-MA20565. Reduction using formic acid as hydrogen source rather than a secondary alcohol gave the best results. The ratio of formic acid to amine was important, and a 1:1 ratio gave the best results for the reduction of *m*-trifluoromethyl acetophenone **2**. The robust nature of this practical process was revealed through successful pilot plant validation on a 100 kg reaction scale.

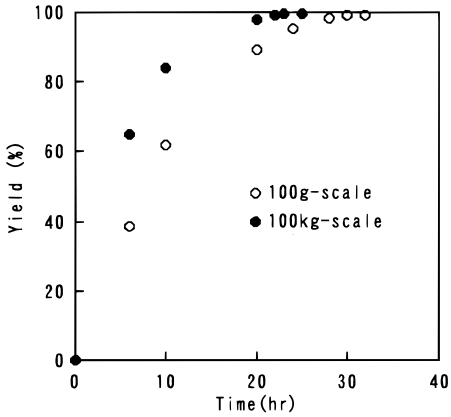


Figure 4. **Effect of scale-up: substrate:formic acid:triethylamine:Ru = 1:2.3:1.3:0.0013.**

Experimental Section

All experiments were performed in glass under a nitrogen atmosphere. 2-Propanol was distilled from calcium hydride. Formic acid (99%) was used as purchased from BASF. Triethylamine was purchased from Wako. (*S*,*S*)-1,2-Diphenylethane-1,2-diamine was purchased from Kankyo Kagaku Center.

The chemical yields and enantiomeric excesses were determined by chiral gas chromatography (Cyclodextrin-β-236M-19, 0.25 mm × 50 M DF = 0.25).

2-PrOH/KOH Method. The ketone **2** (50.0 g, 0.266 mol) and 0.1 M KOH/2-PrOH solution (15 mL, 1.5 mmol) were added to a solution of the ruthenium catalyst **3** (0.339 g, 0.532 mmol) in 2-PrOH (400 mL). The resulting solution was stirred at 25 °C and 45−55 mmHg for 5 h. The yield of the alcohol **1** determined by GC was 99% and the optical purity of **1** determined by chiral GC was 88% ee.

Formic Acid/Triethylamine Method. Formic acid (1.21 g, purity >99%, 26.3 mmol) was added to triethylamine (2.66 g, 26.3 mmol). To this mixture was added the ketone **2** (4.70 g, 25.0 mmol) and a DMF solution (0.1 mmol/mL) of the ruthenium catalyst **3** (0.05 mL, 0.005 mmol). The resulting solution was stirred at 50 °C for 30 h. The yield of **1** determined by GC was 96%, and the optical purity of **1** determined by chiral GC was 91%ee.

Formic Acid/Triethylamine Method (Preparative Scale). Formic acid (134 g, purity >99%, 2.91mol) was added to triethylamine (282 g, 2.79 mol) with cooling in an ice bath. To this mixture was added the ketone **2** (500 g, 2.66 mol) and a DMF (7.0 mL) solution of the ruthenium catalyst **3** (0.891 g, 1.40 mmol). The resulting solution was stirred at 50 °C for 27 h. The final solution was distilled, and the fraction boiling at 87−94 °C/11 mmHg was collected to give the alcohol **1** (498 g, purity >98% by GC, 2.62 mol, 98% yield, 91% ee by chiral GC) as a colorless liquid.

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