Practical Asymmetric Synthesis of (*S*)-MA20565, a Wide-Spectrum Agricultural Fungicide

Ken Tanaka,* Manabu Katsurada,* Fumihiko Ohno, Yasushi Shiga, and Masatsugu Oda

Yokohama Research Center, Mitsubishi Chemical Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama, Kanagawa 227-8502, Japan

Miwa Miyagi, Jun Takehara, and Kazuya Okano*

Tsukuba Research Center, Mitsubishi Chemical Corporation, 8-3-1 Chuo, Ami, Inashiki, Ibaragi 300-0332, Japan

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A practical asymmetric synthesis of a wide-spectrum agricultural fungicide, (*S*)-MA20565 (**1**), is described. The convergent synthesis was achieved starting from commercially available 3-(trifluoromethyl)aniline (**7**) in 44% overall yield through five steps and 2-bromobenzaldehyde (**9**) in 48% overall yield through four steps, respectively. (*S*)-*O*-[1-(3-Trifluoromethylphenyl)ethyl]hydroxylamine (**2**), a key intermediate of **1**, was prepared via ruthenium(II)-catalyzed asymmetric transfer hydrogenation of 1-(3-trifluoromethylphenyl)ethanone (**6**) followed by chlorination using methanesulfonyl chloride and oxyamination using potassium acetohydroxamate with high level of stereocontrol.

Introduction

Strobilurins A and B, a new class of antifungal antibiotics, were first isolated from fermentation of *Strobilurus tenacellus*.[1] Anke et al. reported the fungicidal activities and the mode of action of strobilurins A and B to be respiratory inhibition of mitochondria.[2] To date, many studies have been performed with structural modification of strobilurins.[3] In these studies, Zeneca and BASF groups independently reported the strobilurin analogues ICIA5504[4] and BAS-490F[5] as new class of agricultural fungicides with wide fungicidal spectrum and a new mode of action. These strobilurin variants consist of structurally two modified regions: a pharmacophore and a side chain. ICIA5504 has a methoxyacrylic acid methyl ester as a pharmacophore and a substituted pyrimidine ring side chain.[4] BAS-490F has a methoxyiminoacetic acid methyl ester as a pharmacophore and a substituted phenoxy methyl side chain.[5] Recently, Mitsubishi Chemical group has reported a promising candidate, (*S*)-MA20565 (**1**), bearing an *N*-methylmethoxyiminoacetamide as a pharmacophore and a substituted aldoxime ether side chain, that shows the potent fungicidal activity against wide range of crop diseases.[6] The commercial importance of (*S*)-MA20565 has prompted us to design and develop a practical asymmetric synthesis of the compound.

Results and Discussion

The target compound **1**, which has two oxime ethers and one chiral center at the benzylic position, would be constructed from two key intermediates, an (*S*)-oxyamine **2** and an amide **3**, as shown in Scheme 1. The key transformation in the synthesis is the practical asymmetric synthesis of **2**. The (*S*)-oxyamine **2** was efficiently prepared via enantioselective hydrogenation of 1-(3-trifluoromethylphenyl)ethanone (**6**) followed by chlorination and oxyamination with inversion of the chiral center twice. For the present synthesis, we practically improved Noyori's ruthenium(II)-catalyzed asymmetric transfer hydrogenation[7] using formic acid and triethylamine.[7d] Efficient chlorination, using methanesulfonyl chloride and pyridine in DMF/*n*-heptane, and oxyamination using potassium acetohydroxamate prepared in situ from inexpensive hydroxylamine hydrochloride and acetic an-

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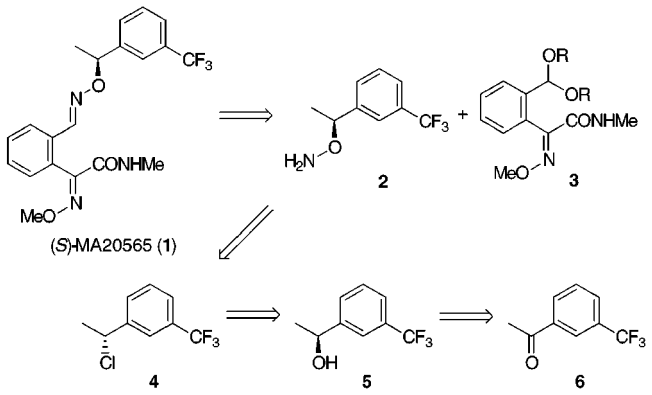
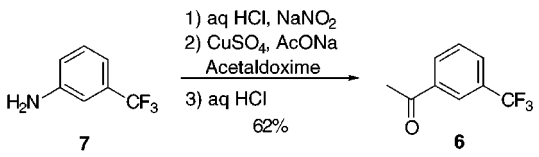
Scheme 1



Scheme 2



hydride were developed with high level of stereocontrol. The synthetic methods will be described in detail in this paper.

Preparation of 1-(3-Trifluoromethylphenyl)ethanone (6). A Grignard reaction of aryl bromide and acetic anhydride is one of the practical choice for the preparation of acetophenone derivatives.[8] However, this reaction could not be applied to the synthesis of **6** due to high explosibility of a Grignard reagent prepared from 3-bromobenzotrifluoride.[9] Beech reaction[10] was the method of choice because of its safe operation and the low cost of 3-(trifluoromethyl)aniline (**7**).[11] Thus, the diazonium salt of **7** was treated with acetaldoxime in the presence of AcONa and $CuSO_4$ followed by treatment with aqueous HCl to give **6** in 62% yield (Scheme 2).

Preparation of (*S*)-*O*-[1-(3-Trifluoromethylphenyl)ethyl]hydroxylamine (2). To access an (*S*)-alcohol **5**, Noyori's ruthenium(II)-catalyzed asymmetric transfer hydrogenation of 1-(3-trifluoromethylphenyl)ethanone (**6**) was examined from the practical point of view such as no need of an expensive high-pressure autoclave, safeness of operations, low cost of catalyst, and getting high optical purity.[7]

In the first attempt, *i*-PrOH was used as the hydrogen source.[7a] To a solution of the ruthenium catalyst **8**[7f] [substrate/catalyst (S/C) mole ratio = 500], *i*-PrOH, and KOH was added the ketone **6**, and the resulting mixture (0.66 M concentration of **6**) was stirred at reduced pressure (45−55 mmHg) to give **5** in 99% yield with 88% ee (Scheme 3). As the reverse reaction with acetone caused the decline of the yield and the optical purity of **5**, in the reaction at atmospheric pressure, the employment of lower concentration (0.1 M) gave **5** in higher yield (up to 97%) and optical purity (90−91% ee). On the other hand, the employment of higher concentration (1 M) gave

Scheme 3

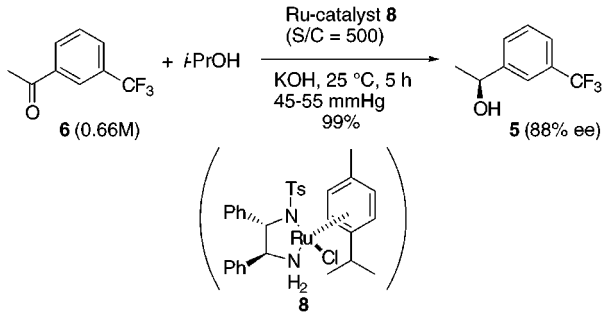
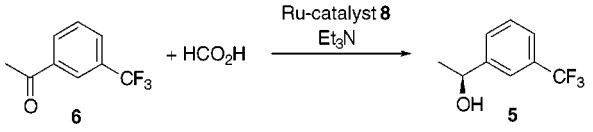


Table 1. Asymmetric Transfer Hydrogenation of 6 with Formic Acid[a]



entry	S/C	HCO_2H (equiv)	Et_3N (equiv)	*T* (°C)	time (h)	yield[b] (%)	ee[b] (%)
1[c]	200	11.5	4.6	25	24	66	94
2[c]	500	11.5	4.6	25	25	8	
					46	37	93
					77	95	95
3	1000	1.05	1.05	25	24	99	93
4	5000	1.05	1.05	50	30	96	91

[a] The ketone **6** (10 g) was used. [b] Determined by GC. [c] HCO_2H−Et_3N (5:2) azeotrope was used.

5 in lower yield (<94%) and optical purity (88−89% ee).[12] The removal of acetone at reduced pressure could raise the yield of **5** and keep the optical purity of **5**; however, this operation was not practical due to small difference of boiling point between acetone and *i*-PrOH.

To achieve the hydrogenation in higher concentration, formic acid was examined as hydrogen source to avoid reverse reaction.[7f] Although the use of triethylammonium formate was attractive on the point of the optical purity (94% ee), the reaction rate was very low (Table 1, entry 1). A detailed investigation of the time-course of the alcohol formation revealed the induction period before the main acceleration of the reaction (Table 1, entry 2). We found that a slight excess formic acid to the substrate was sufficient to complete the reaction, and excess base against the formic acid is necessary to keep high reaction rate (Table 1, entry 3). Under the optimum reaction conditions, the reaction completely proceeded under S/C = 5000 to give **5** in 96% yield with 91% ee (Table 1, entry 4). Direct fractional distillation of the reaction mixture could be employed to give pure **5** and triethylamine, which could be reused.

A direct amination of the (*S*)-alcohol **5** with NH_2Cl[13] or NH_2OSO_3H[14] was examined, but the desired (*S*)-oxyamine **2** was not obtained at all. Therefore, two-step operations were examined via a (*R*)-chloride **4**. The preparation of **4** from **5** was investigated as summarized in Table 2, using enantiopure **5** prepared by lipase-catalyzed transesterification with vinyl laurate using TOYOZYME LIP (*Pseudomonas* sp.). The use of $SOCl_2$

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(10) Beech, W. F. *J. Chem. Soc.* **1954**, 1297.

(11) Aldrich catalog (1998−1999, Japan): 3-bromobenzotrifluoride; 11 000 yen (100 g), 3-(trifluoromethyl)aniline; 4900 yen (100 g).

(12) Recently, asymmetric transfer hydrogenation of **6** was improved up to 97% ee by chiral rhodium complex. Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186.

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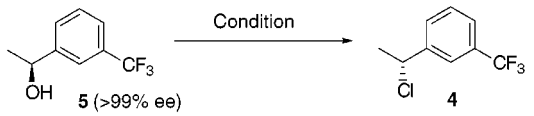
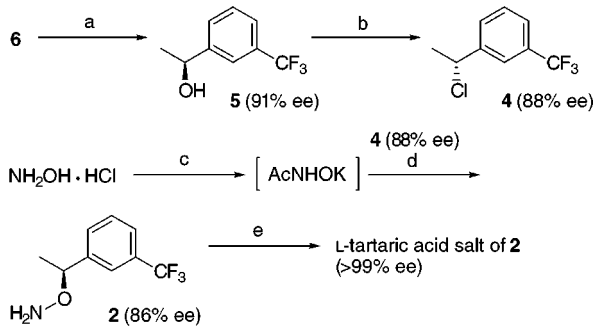
Table 2. Chlorination of 5 in Various Reaction Conditions



entry	conditions	time (h)	yield[a] (%)	ee[a] (%)
1[b]	$SOCl_2$, Py, DMF (cat), *t*-BuOMe	8	87	74
2[c]	MsCl, Py	24	99	96
3[b]	MsCl, Py, DMF	3 (24)	88 (99)	90 (86)
4[b]	MsCl, Py, NMP	24	8	86
5[b]	MsCl, Py, DMF/*i*-Pr_2O (2:5)	15	96	96
6[b]	MsCl, Py, DMF/*i*-Pr_2O (1:50)	8	7	96
7[b]	MsCl, Py, DMF/*n*-Heptane (2:5)	3	96	96

[a] Determined by GC. [b] To a solution of **5** (1.0 g, >99% ee), pyridine (1.1 equiv), and solvent (50 mL) was added $SOCl_2$ or MsCl (1.1 equiv) at 0 °C, and the mixture was stirred at 25 °C. [c] Pyridine (5.0 mL) was used.

Scheme 4[a]

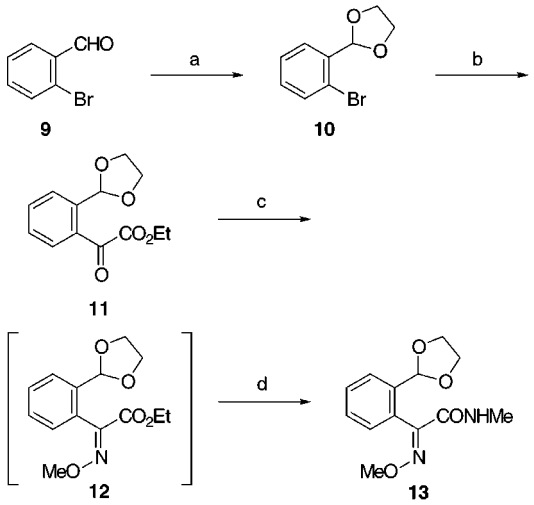


[a] Key: (a) HCO_2H, Et_3N, **8** (S/C = 1900), 50 °C, 98%, 91% ee; (b) MsCl, Py, DMF/*n*-heptane [1:9 (v/v)], 25 °C, 96%, 88% ee; (c) Na_2CO_3, Ac_2O, KOH, EtOH/H_2O, 25 °C; (d) (1) *n*-Bu_4NBr, 70 °C, (2) concd HCl, 70 °C, (3) neutralization and distillation, 80% from **4**, 86% ee; (e) crystallization with L-tartaric acid from THF/*i*-Pr_2O, 70%, >99% ee.

and pyridine gave **4** in modest yield and optical purity (87%, 74% ee; Table 2, entry 1). On the other hand, the use of methanesulfonyl chloride in pyridine increased the yield and optical purity of **4** (99%, 96% ee; Table 2, entry 2). When the chlorination was carried out in DMF, the amount of pyridine could be reduced to 1.1 equiv, but the optical purity of **4** was gradually decreased during the reaction period (Table 2, entry 3). The use of 1-methyl-2-pyrrolidinone (NMP) in place of DMF decreased the reaction rate (Table 2, entry 4). To avoid the racemization of **4**, the less polar solvents which hardly dissolve pyridine hydrochloride was partially employed in place of DMF. Thus, the chlorination was carried out in DMF/*i*-Pr_2O [2:5 (v/v)] to give **4** in 96% yield and 96% ee along with higher reaction rate (Table 2, entry 5). Further reduction of the amount of DMF [DMF/*i*-Pr_2O = 1:50 (v/v)] decreased the reaction rate (Table 2, entry 6). Finally, the use of DMF/*n*-heptane [2:5 (v/v)] showed the highest reaction rate, which allowed the simple operations and low load of waste treatments (Table 2, entry 7).

The (*S*)-oxyamine **2** was prepared from **6** in a large scale as shown in Scheme 4. To a solution of the ruthenium catalyst **8** (S/C = 1900), 1.09 equiv of formic acid, and 1.05 equiv of triethylamine was added the ketone **6**, and the solution was stirred at 50 °C for 27 h. The resulting solution was distilled to give the (*S*)-alcohol **5** in 98% yield with 91% ee. The (*S*)-alcohol **5** was treated

Scheme 5[a]



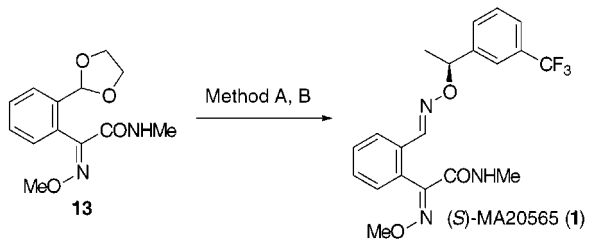
[a] Key: (a) ethylene glycol, *p*-toluenesulfonic acid, toluene, reflux, 97%; (b) (1) Mg, THF, (2) diethyl oxalate, toluene/THF, <−2 °C, (3) aqueous HCl, 0-8 °C, pH 6-7, 83%; (c) CH_3ONH_2·HCl, *N*,*N*-diethylaniline, EtOH, 25 °C; (d) (1) 40% aqueous CH_3NH_2, 25 °C, (2) crystallization from *n*-heptane/*N*,*N*-diethylaniline, 64% from **11** (*E*/*Z* = 98:2).

with 1.1 equiv of methanesulfonyl chloride and 1.1 equiv of pyridine in DMF/*n*-heptane [1:9 (v/v)] to give the (*R*)-chloride **4** in 96% yield with 88% ee. The (*R*)-chloride **4** was treated with *n*-Bu_4NBr and potassium acetohydroxamate prepared in situ from hydroxylamine hydrochloride, Na_2CO_3, acetic anhydride, and KOH followed by the treatment with aqueous HCl to give the crude (*S*)-oxyamine **2**. The crude **2** was purified by distillation to give **2** in 80% yield from **4** with >98% purity and 86% ee. Furthermore, the enantioenriched **2** (86% ee) could be purified by the crystallization with L-tartaric acid from THF/*i*-Pr_2O to give an L-tartaric acid salt of **2** in 70% yield with >99% ee.[15]

Preparation of Amide 13. An amide **13** was prepared from 2-bromobenzaldehyde (**9**) in three steps as shown in Scheme 5. The aldehyde **9** was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid employing azeotropic dehydration followed by distillation to give an acetal **10** in 97% yield. A Grignard reagent prepared from **10** was added to a solution of diethyl oxalate and toluene at below −2 °C followed by hydrolysis with aqueous HCl at 0−8 °C (pH 6−7) to give a crude ketoester **11** in 83% yield. The oxime ether formation from **11** was investigated with methoxylamine hydrochloride and base. It was consequently found that base was crucial for the success of this transformation. The best base, by far, was *N*,*N*-diethylaniline, which could minimize the deprotection of acetal. Thus, the crude ketoester **11** was treated with 1.5 equiv of methoxylamine hydrochloride in the presence of 1.65 equiv of *N*,*N*-diethylaniline at 25 °C for 24 h to generate an oxime ether **12** (*E*/*Z* = 86:14). The oxime ether **12** was subsequently treated with 40% aqueous CH_3NH_2 without isolation. After distillation of methanol, the crude mixture was crystallized by the addition of *n*-heptane and water to give **13** in 64% yield

(15) Though the resolution of **2** with D-tartaric acid in MeOH/H_2O was more effective than L-tartaric acid in THF/*i*-Pr_2O, L-tartaric acid was selected due to higher cost of D-tartaric acid. Aldrich catalog (1998−1999, Japan): D-tartaric acid; 7800 yen (99% ee, 100 g), L-tartaric acid; 2700 yen (99% ee, 500 g).

Scheme 6[a]



[a] Method A: AcOH/H_2O [1:2 (v/v)], 2 (86% ee), 94% from **13**, 86% ee. Method B: AcOH/H_2O [1:2 (v/v)], L-tartaric acid salt of **2** (>99% ee), 96% from **13**, >99% ee.

with >99% purity and high *E*/*Z* isomer ratio (*E*/*Z* = 98:2).[16] In this process, *N*,*N*-diethylaniline was highly efficient as not only the base but also the crystallization solvent, which could selectively dissolve the (*Z*)-amide (*Z*)-**13**. The use of diethyl acetal instead of 1,3-dioxolane as the protective group showed the complete decomposition of the acetal group in the treatment with methoxylamine hydrochloride. The use of 1,3-dioxane, which is more tolerable than 1,3-dioxolane in this acidic reaction condition, showed lower *E*/*Z* isomer ratio (90:10) of the amide **3** after crystallization.

Condensation of (*S*)-Oxyamine 2 and Amide 13. The condensation of the (*S*)-oxyamine **2** and the amide **13** was investigated using various acids. In the presence of strong acids, such as HCl or H_2SO_4, decomposition of a condensation product **1** was significantly occurred. On the other hand, the use of acetic acid could minimize the decomposition of **1**. Furthermore, it was found that the addition of water to this reaction fairly accelerated the reaction rate and could directly crystallize **1** from the reaction mixture. Thus, the amide **13** (*E*/*Z* = 98:2) and 1.07 equiv of the (*S*)-oxyamine **2** (86% ee) was treated in acetic acid/H_2O [1:2 (v/v)] and the crystallization was directly carried out from the reaction mixture followed by washing with hot water to give (*S*)-MA20565 (**1**) in 94% yield from **13** with >98% purity (*E*/*Z* > 99.5:0.5) and 86% ee. In this reaction, the equilibration of a (*Z*)-aldoxime ether and an (*E*)-aldoxime ether was observed,[17] however, the (*E*)-aldoxime ether was selectively crystallized from this reaction mixture to give **1** in high *E*/*Z* isomer ratio (*E*/*Z* > 99.5:0.5).[18] Alternatively, the amide **13** (*E*/*Z* = 98:2) and 1.02 equiv of L-tartaric acid salt of **2** (>99% ee) was treated in acetic acid/H_2O [1:3 (v/v)], and the crystallization was directly carried out from the reaction mixture followed by washing with hot water to give **1** in 96% yield from **13** with >98% purity (*E*/*Z* > 99.5:0.5) and >99% ee (Scheme 6).

Summary

In conclusion, an asymmetric synthesis of enantioenriched (*S*)-MA20565 (**1**) was achieved starting from commercially available 3-(trifluoromethyl)aniline (**7**) and 2-bromobenzaldehyde (**9**) in an overall yield of 44% and 48%, respectively, with an enantiomeric excess of 86%. The enantiopure **1** was also synthesized by the crystallization of the enantioenriched (*S*)-oxyamine **2** with L-tartaric acid followed by condensation with the amide **13**. This method is highly attractive for a large-scale preparation of **1** and is expected to contribute to the development of this novel agricultural fungicide because of the simple operations and the use of inexpensive reagents.

Experimental Section

General Methods. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were collected at 300 MHz. Reactions and purities were determined by HPLC [column: Inertsil ODS-2, column temperature 40 °C, eluent: MeOH/H_2O (75:25); 1.0 mL/min, detect: 254 nm] or GC (column: DB-1; 0.25 mm × 25 m, detector: FID, carrier gas: He) using biphenyl as an internal standard unless otherwise noted. Chiral HPLC were run with CHIRALCEL OJ column [eluent: *n*-hexane/*i*-PrOH (80:20); 1.0 mL/min, detect: 220 nm]. Chiral GC were run with CHROMPACK Cyclodextrin-*β*-236M-19 column (0.25 mm × 50 m, detector: FID, carrier gas: He). Specific rotations were recorded on a JASCO DIP-370 polarimeter in the indicated solvent. All reagents were plant grade and used without further purification. Formic acid (purity >99%) was purchased from BASF AG. TOYOZYME LIP was purchased from TOYOBO Co. The ruthenium catalyst (**8**)[7f] and (±)-1-(3-trifluoromethylphenyl)ethanol[9] were prepared according to the literature.

1-(3-Trifluoromethylphenyl)ethanone (6). To a mixture of 3-(trifluoromethyl)aniline (**7**) (20.0 g, 0.124 mol), H_2O (60 mL), and concentrated HCl (32.0 g, 0.325 mol) was added $NaNO_2$ (9.4 g, 0.136 mol) at −5−0 °C, and the mixture was stirred at −5 to 0 °C for 20 min. The resulting mixture was added to a solution of acetaldoxime (14.8 g, 0.251 mol), $CuSO_4$ (6.6 g, 41 mmol), and $AcONa{\cdot}3H_2O$ (90.0 g, 0.661 mol) at 0−10 °C, and the mixture was stirred at 10−15 °C for 1.5 h. To the resulting mixture was added concentrated HCl (55 mL), and the mixture was refluxed for 2 h. The mixture was cooled to 25 °C and extracted with *n*-heptane (20 mL). The organic layer was separated and washed with water. The solvent was removed under reduced pressure, and the residue was purified by distillation to give **6** (14.5 g, 77.1 mmol, purity >98% by GC, 62% yield) as a colorless liquid: bp 96−99 °C/23 mmHg (lit.[19] bp 198−200 °C); IR (neat) 1685, 1327, 1119 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.61 (3H, s), 7.58 (1H, t, *J* = 7.8 Hz), 7.78 (1H, d, *J* = 7.8 Hz), 8.10 (1H, d, *J* = 7.8 Hz), 8.17 (1H, s); ^{13}C NMR ($CDCl_3$) *δ* 26.48, 123.69, 125.04, 129.28, 129.44, 131.19, 131.44, 137.54, 196.55.

(*S*)-1-(3-Trifluoromethylphenyl)ethanol (5): *i*-PrOH/KOH Method. The ketone **6** (50.0 g, 0.266 mol) and 0.1 M KOH/*i*-PrOH solution (15 mL, 1.5 mmol) was added to a solution of *i*-PrOH (400 mL) and the ruthenium catalyst **8** (0.339 g, 0.532 mmol), and the resulting solution was stirred at 25 °C and 45−55 mmHg for 5 h. The yield of **5** determined by GC was 99%, and the optical purity of **5** determined by chiral GC was 88% ee.

(*S*)-1-(3-Trifluoromethylphenyl)ethanol (5): HCO_2H/Et_3N Method. Formic acid (134 g, purity >99%, 2.91 mol) was added to triethylamine (282 g, 2.79 mol) by cooling with an ice bath. To the solution was added **6** (500 g, 2.66 mol) and a DMF (7.0 mL) solution of the ruthenium catalyst **8** (0.891 g, 1.40 mmol), and the resulting solution was stirred at 50 °C for 27 h. The resulting solution was distilled, and the fraction boiling at 87−94 °C/11 mmHg was collected to give **5** (498 g, purity >98% by GC, 2.62 mol, 98% yield, 91% ee by chiral GC) as a colorless liquid.

(*S*)-1-(3-Trifluoromethylphenyl)ethanol (5): Lipase-Catalyzed Resolution. A mixture of (±)-1-(3-trifluoromethylphenyl)ethanol (300 g, 1.58 mol), TOYOZYME LIP (100 g), vinyl laurate (252 g, 1.11 mol), and *i*-Pr_2O (1000 mL) was stirred at 25 °C for 5 h. The reaction mixture was filtered and concentrated in vacuo. The residue was extracted with MeOH/H_2O [7:1 (v/v), 1000 mL] twice, and MeOH was removed at

(16) *N*,*N*-Diethylaniline and *n*-heptane could be recycled by fractional distillation of the filtrate.

(17) *E*/*Z* isomer ratio of the aldoxime ether group of **1** in the solution of acetic acid/H_2O [2:1 (v/v)] was 95:5.

(18) (*Z*)-Ketoxime ethers were not detected at all by HPLC.

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reduced pressure. The lower organic layer was separated and distilled through a Vigreux distilling column, and the fraction boiling at 73−74 °C/3.2 mmHg was collected to give pure **5** (103 g, purity >99% by GC, 0.542 mol, 34% yield, >99% ee by chiral GC) as colorless liquid: $[\alpha]^{22}_D$ −27.9 (*c* 1.64, CH_3OH, >99% ee) [lit.[20] $[\alpha]^{22}_D$ −18.0 (*c* 1.67, CH_3OH, 66% ee)]; IR (neat) 3336, 1325, 1117 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (3H, d, J = 6.6 Hz), 2.73 (1H, br), 4.89 (1H, q, J = 6.6 Hz), 7.40−7.52 (3H, m), 7.61 (1H, m); ^{13}C NMR ($CDCl_3$) δ 25.24, 69.73, 122.17, 124.16, 124.19, 128.79, 128.90, 130.75, 146.75.

(*R*)-1-Chloro-1-(3-trifluoromethylphenyl)ethane (4). To a solution of **5** (100 g, purity >98% by GC, 0.526 mol, 91% ee by chiral GC), pyridine (45.8 g, 0.579 mol), DMF (25 mL), and *n*-heptane (225 mL) was added methanesulfonyl chloride (66.3 g, 0.579 mol), keeping the temperature below 5 °C, and the resulting mixture was stirred at 25 °C for 9 h. The mixture was washed with 1 M aqueous HCl, 5% aqueous $NaHCO_3$, and 20% aqueous NaCl. The solvent was removed under reduced pressure to give **4** (110 g, purity 96% by GC, 0.506 mol, 96% yield, 88% ee by chiral GC) as a pale yellow liquid. An analytically pure sample was obtained by fractional distillation as colorless liquid: bp 68−69 °C/8.0 mmHg; $[\alpha]^{22}_D$ +48.7 (*c* 0.930, $CHCl_3$, 88% ee); IR (neat) 1325, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (3H, d, J = 6.9 Hz), 5.10 (1H, q, J = 6.9 Hz), 7.44−7.62 (3H, m), 7.67 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.73, 82.06, 123.04, 124.20, 124.43, 128.98, 129.67, 130.88, 144.50. Anal. Calcd for $C_9H_8ClF_3$: C, 51.82; H, 3.87. Found: C, 51.72; H, 3.52.

(*S*)-*O*-[1-(3-Trifluoromethylphenyl)ethyl]hydroxylamine (2). To a mixture of H_2O (75 mL), EtOH (75 mL), and Na_2CO_3 (138 g, 1.30 mol) was added hydroxylamine hydrochloride (80.4 g, 1.16 mol), and the resulting mixture was stirred at 35 °C for 20 min. To the mixture were added acetic anhydride (132 g, 1.29 mol) and subsequently EtOH (100 mL), and the resulting mixture was stirred at 40 °C for 2 h. To the mixture were added 95% solid KOH (84.9 g, 1.44 mmol) and *n*-Bu_4NBr (1.5 g, 4.65 mmol), and subsequently a solution of **4** (120 g, purity 96% by GC, 0.553 mol, 88% ee by chiral GC) and EtOH (50 mL), and the resulting mixture was stirred at 70 °C for 6 h. After the mixture was cooled to 0 °C, concentrated HCl (420 g, 4.26 mol) was added to the mixture, and the resulting mixture was stirred at 50 °C for 2 h. After the mixture was cooled to 25 °C, H_2O (120 mL) and *n*-heptane (100 mL) were added to the mixture, and the organic layer was removed. The separated water layer was adjusted at pH 7 with aqueous NaOH and re-extracted with *n*-heptane (180 mL). The organic layer was separated and washed with H_2O and brine. The solvent was removed under reduced pressure followed by distillation to give **2** (93.0 g, purity 98% by GC, 0.444 mol, 80% yield from **4**, 86% ee by chiral GC) as a colorless liquid boiling at 59.5−61 °C/2.0 mmHg.

Resolution of (*S*)-*O*-[1-(3-Trifluoromethylphenyl)ethyl]hydroxylamine (2) with L-Tartaric Acid. To a solution of **2** (4.10 g, purity 98% by GC, 19.6 mmol, 86% ee by chiral GC), THF (24.0 mL), and *i*-Pr_2O (4.0 mL) was added L-tartaric acid (3.0 g, 20.0 mmol), and the resulting mixture was refluxed to give a colorless solution. The solution was cooled to 25 °C, and the resulting slurry was filtered. The product was dried in vacuo to give L-tartaric acid salt of **2** (4.90 g, 13.8 mmol, 70% yield, >99% ee by GC after neutralization with NaOH) as a white crystalline solid: mp 138.7−138.8 °C; $[\alpha]^{22}_D$ −44.3 (*c* 1.19, CH_3OH); IR (neat) 2945, 2590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29 (3H, d, J = 6.6 Hz), 4.29 (2H, s), 4.64 (1H, q, J = 6.6 Hz), 7.53−7.64 (4H, m); ^{13}C NMR (DMSO-d_6) δ 22.25, 72.61, 80.90, 123.09, 124.31, 126.62, 129.41, 129.72, 130.73, 146.12, 173.60. Anal. Calcd for $C_{13}H_{16}F_3NO_7$; C, 43.95; H, 4.54; N, 3.94. Found: C, 44.23; H, 4.33; N 3.78.

An analytically pure **2** was obtained by neutralization of L-tartaric acid salt of **2** (>99% ee) with aqueous NaOH and distillation as colorless liquid: $[\alpha]^{22}_D$ −58.9 (*c* 0.986, $CHCl_3$, >99% ee); IR (neat) 1327, 1117 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3H, d, J = 6.6 Hz), 4.72 (1H, q, J = 6.6 Hz), 5.30 (2H, br), 7.44−7.56 (3H, m), 7.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.73, 82.06, 123.04, 124.20, 124.43, 128.98, 129.67, 130.88, 144.50. Anal. Calcd for $C_9H_{10}F_3NO$; C, 52.69; H, 4.91; N, 6.83. Found: C, 52.41; H, 4.62; N, 6.86.

2-(2-Bromophenyl)-1,3-dioxolane (10).[21] A solution of **9** (463 g, 2.50 mol), *p*-toluenesulfonic acid monohydrate (4.76 g, 0.025 mol), ethylene glycol (310 g, 4.99 mol), and toluene (2500 mL) was refluxed for 9 h employing azeotropic dehydration. After the solution was cooled to 25 °C, aqueous $NaHCO_3$ was added, and the organic layer was separated and washed with water. The solvent was removed under reduced pressure followed by distillation to give **10** (557 g, purity >99% by GC, 2.43 mol, 97% yield) as colorless liquid: bp 126−127 °C/5.0 mmHg; IR (neat) 2887, 1084 cm^{-1}; ^1H NMR (CDCl3) δ 4.00−4.14 (4H, m), 6.08 (1H, s), 7.16−7.22 (1H, m), 7.28−7.34 (1H, m), 7.53−7.60 (2H, m); ^{13}C NMR ($CDCl_3$) δ 65.50, 102.64, 122.98, 127.47, 127.90, 130.67, 133.00, 136.70.

Ethyl 2-[2-(1,3-Dioxolan-2-yl)phenyl]-2-oxoacetate (11). To a mixture of THF (1080 mL) and Mg (58.0 g, 2.39 mol) were added a Grignard reagent of **10** prepared from Mg (3.05 g, 0.125 mol), THF (57 mL), **10** (28.5 g, 0.124 mol), and I_2 (0.1 g) at 20−24 °C and subsequently **10** (542 g, 2.36 mol) at 35−45 °C. The resulting mixture was stirred at 67−68 °C for 1 h followed by cooling to 25 °C. The mixture was added to a solution of toluene (3020 mL) and diethyl oxalate (725 g, 4.96 mol) below −2 °C, and the mixture was stirred at 5−8 °C for 1 h. The resulting mixture was added to a solution of concentrated aqueous HCl (140 g) and H_2O (1400 mL) at 0−8 °C, and the organic layer was separated and washed with aqueous $NaHCO_3$ and 20% aqueous NaCl. The solvent and excess diethyl oxalate were removed under reduced pressure to give crude **11** (613 g, 2.06 mol, purity 84% by GC, 83% yield) as yellow oil, which was used in the next step without further purification. An analytically pure sample was obtained by recrystallization from MeOH as a white crystalline solid: mp 45−46 °C; IR (neat) 2981, 1732, 1707, 1196 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.2 Hz), 3.80−3.98 (4H, m), 4.37 (2H, q, J = 7.2 Hz), 7.41−7.61 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.00, 62.38, 64.64, 101.65, 126.67, 128.84, 129.37, 131.85, 134.34, 138.91, 161.82, 188.13. Anal. Calcd for $C_{13}H_{14}O_5$; C, 62.39; H, 5.64. Found: C, 62.01; H, 5.61.

(*E*)-2-[2-(1,3-Dioxolan-2-yl)phenyl]-2-methoxyimino-*N*-methylacetamide [(*E*)-13] and (*Z*)-2-[2-(1,3-Dioxolan-2-yl)phenyl]-2-methoxyimino-*N*-methylacetamide [(*Z*)-13]. A solution of crude **11** (35.8 g, purity 84% by GC, 0.120 mol), *N*,*N*-diethylanilline (29.5 g, 0.198 mol), methoxylamine hydrochloride (15.0 g, 0.180 mol), and methanol (30 mL) was stirred at 25 °C for 24 h. The resulting methanol solution contained mainly (*E*)-2-[2-(1,3-dioxolan-2-yl)phenyl]-2-methoxyimino-*N*-methylacetamide [(*E*)-**12**] and (*Z*)-2-[2-(1,3-dioxolan-2-yl)phenyl]-2-methoxyimino-*N*-methylacetamide [(*Z*)-**12**] (*E*/*Z* = 86:14 by GC). An analytically pure sample of (*E*)-**12** was obtained by conventional workup and recrystallization from *n*-hexane/EtOAc as a white crystalline solid: mp 84.5−85.5 °C; IR (neat) 2983, 2941, 2898, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.2 Hz), 3.93−3.98 (4H, m), 4.01 (3H, s), 4.32 (2H, q, J = 7.2 Hz), 5.78 (1H, s), 7.14−7.19 (1H, m), 7.38−7.44 (2H, m), 7.54−7.58 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.15, 61.89, 63.59, 65.00, 102.56, 126.87, 128.76, 128.83, 129.06, 129.80, 135.96, 150.51, 163.12. Anal. Calcd for $C_{14}H_{17}NO_5$; C, 60.21; H, 6.14; N, 5.02. Found: C, 60.19; H, 6.38; N 4.73.

Aqueous methylamine (40%, 46.6 g, 0.60 mol) was added to the methanol solution, and the resulting mixture was stirred at 25 °C for 2 h. Methanol was removed under reduced pressure, and the mixture was diluted with *n*-heptane (100 mL) and H_2O (100 mL) followed by heating at 60 °C for 30 min. The mixture was cooled to 0 °C, and the resulting slurry was filtered. The product was washed with *n*-heptane (25 mL) and dried in vacuo to give **13** [20.4 g, purity >99% by GC, 77.2 mmol, 64% yield, *E*/*Z* = 98:2 by GC (column: DB-17ht; 0.25

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mm × 30 m, detector: FID, carrier gas: He)] as a white crystalline solid: mp 104−108 °C; ^{1}H NMR ($CDCl_3$) δ 2.89 [3H, d, J = 5.1 Hz, (*Z*)-isomer], 2.92 [3H, d, J = 5.1 Hz, (*E*)-isomer], 3.94 [7H, s, (*E*)-isomer)], 4.01 [3H, s, (*Z*)-isomer], 4.03 [4H, s, (*Z*)-isomer], 5.87 [1H, s, (*E*)-isomer], 6.25 [1H, s, (*Z*)-isomer], 6.74 (1H, br), 7.14−7.17 (1H, m), 7.39−7.44 (2H, m), 7.59−7.62 (1H, m). An analytically pure sample of (*E*)-**13** was obtained by washing with *n*-BuOH as a white crystalline solid: mp 111−112 °C; IR (neat) 3358, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90 (3H, d, J = 5.1 Hz), 3.93 (7H, s), 5.86 (1H, s), 6.75 (1H, br), 7.13−7.16 (1H, m), 7.38−7.41 (2H, m), 7.58−7.61 (1H, m); ^{13}C NMR ($CDCl_3$) δ 26.23, 63.19, 64.86, 102.04, 126.19, 128.59, 128.71, 129.11, 136.73, 151.81, 163.15. Anal. Calcd for $C_{13}H_{16}N_2O_4$; C, 59.08; H, 6.10; N, 10.60. Found: C, 59.02; H, 6.14; N 10.50.

(*E*,*E*)-(*S*)-2-(Methoxyimino)-*N*-methyl-2-[2-[[1-(3-trifluoromethylphenyl)ethoxyimino]methyl]phenyl]-acetamide [(*S*)-MA20565] (1). Method A. To a solution of **2** (24.6 g, purity 98% by GC, 0.117 mol, 86% ee), acetic acid (56 mL), and H_2O (112 mL) was added **13** (28.9 g, purity >99% by GC, 0.109 mol, E/Z = 98:2 by GC), and the mixture was stirred at 30−35 °C for 1 h. Seed crystals of **1** were added to the mixture, and the resulting slurry was stirred at 30−35 °C for another 5 h. The slurry was aged at 25 °C for 12 h and at 30−35 °C for 6 h. The product was filtered, washed with hot water three times, and dried in vacuo to give **1** [41.6 g, purity >98% by HPLC, 0.102 mol, 94% yield from **13**, 86% ee by chiral HPLC, (*E*)-aldoxime ether:(*Z*)-aldoxime ether >99.5:0.5 by HPLC (column: Inertsil ODS-2, column temperature 40 °C, eluent: MeOH/H_2O (60:40); 1.0 mL/min, detect: 254 nm, retention time; (*E*)-aldoxime ether: 24.6 min; (*Z*)-aldoxime ether: 20.0 min); (*Z*)-ketoxime ether was not detected] as a white crystalline solid: mp 83−85 °C.

(*E*,*E*)-(*S*)-2-(Methoxyimino)-*N*-methyl-2-[2-[[1-(3-trifluoromethylphenyl)ethoxyimino]methyl]phenyl]-acetamide [(*S*)-MA20565] (1). Method B. To a solution of L-tartaric acid salt of **2** (2.74 g, 7.71 mmol, >99% ee), acetic acid (3.0 mL), and water (9.0 mL) was added **13** (2.00 g, 7.57 mmol, E/Z = 98:2 by GC), and the mixture was stirred at 25 °C for 4 h and at 50 °C for 4 h. The resulting slurry was cooled to 25 °C and filtered. The product was washed with hot water and dried in vacuo to give **1** (2.97 g, purity >98% by HPLC, 7.29 mol, 96% yield from **13**, >99% ee by chiral HPLC, E/Z > 99.5:0.5 by HPLC) as a white crystalline solid. An analytically pure sample was obtained by recrystallization from *n*-hexane/EtOAc as a white crystalline solid: mp 89−90 °C; $[\alpha]^{22}_D$ −42.7 (*c* 1.00, $CHCl_3$); IR (neat) 3410, 3371, 2989, 2943, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (3H, d, J = 6.6 Hz), 2.87 (3H, d, J = 5.1 Hz), 3.85 (3H, s), 5.31 (1H, q, J = 6.6 Hz), 6.68 (1H, br), 7.13−7.16 (1H, m), 7.34−7.55 (5H, m), 7.60 (1H, s), 7.66−7.69 (1H, m), 7.96 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.83, 26.15, 63.25, 80.70, 123.13, 124.22, 124.31, 127.19, 128.84, 129.20, 129.28, 129.32, 129.42, 129.84, 130.27, 130.64, 144.37, 147.70, 150.53, 162.77. Anal. Calcd for $C_{20}H_{20}F_3N_3O_3$; C, 58.97; H, 4.95; N, 10.31. Found: C, 58.90; H, 4.55; N 10.41.

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