Catalytic Asymmetric Syntheses of ICI-199441 and CP-99994 Using Nitro-Mannich Reaction

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Catalytic asymmetric syntheses of ICI-199441 and CP-99994 were achieved using the nitro-Mannich reaction as a key step.

1,2-Diamines[1] are abundantly present in biologically active compounds. ICI-199441 (**1**)[2] and CP-99994 (**2**)[3] are examples of such compounds with clinically appealing activities (Figure 1). Compound **1** is a highly potent κ-opioid agonist, which is expected to provide useful analgesics without the serious side effects of μ-agonists like morphine, and **2** is a competent antagonist of substance P, which is implicated in the pathogenesis of a variety of inflammatory diseases. Moreover, **2** also inhibits the emetic response[4] and might be useful for controlling emesis evoked by chemotherapy against cancer. Although definite pharmacophore models of these two compounds have not yet been clarified, the orientation of the amino groups is very important. Thus, enantioselective synthesis is strongly desirable. All syntheses reported to date[2a,b,3a,d] commence from readily available chiral-pool organic substrates like amino acids that are converted to 1,2-diamines by transformation of hydroxyl or carboxyl groups to an amino group.

We recently developed the catalytic asymmetric addition of nitroalkanes to imines, referred to as the nitro-Mannich reaction. This reaction provides chiral β-nitroamines, which are easily converted to chiral 1,2-diamines.[5,6] We, therefore, attempted to develop more straightforward and flexible routes to **1** and **2**. Herein, we report the catalytic asymmetric syntheses of **1** and **2** utilizing the nitro-Mannich reaction.

Our plans for the syntheses are outlined in the Figure 1. Compounds **1** and **2** can be traced to chiral β-nitroamines **3** and **4** respectively, which are produced by the catalytic asymmetric nitro-Mannich reaction. Although **4** was expected to have an undesirable stereochemistry (*S*, *R*) based on previously obtained results,[6b] we planned to obtain the desirable isomer by epimerization.

The synthesis of **1** is summarized in Scheme 1. The catalytic asymmetric nitro-Mannich reaction of benzaldehyde imine **6** was performed at $-40\,^{\circ}$C in the presence of $YbKH_2$[(*R*)-binaphthoxide]$_3$ (**8**) (20 mol%)[7] with nitromethane (**5**) added over 27 h, to give the nitroamine **3** in 79% yield with 91% ee,[6a,8] which was converted to an enantiomerically pure form (>99% ee) in 78% yield upon recrystallization from MeOH.[9] After the nitro group was reduced in 92% yield using Raney nickel, the pyrrolidine ring was constructed in 81% yield by reductive alkylation. The cleavage of the diphenylphosphinoyl group was realized under mildly acidic conditions, cleanly affording diamine **10** in 98% yield. Reductive methylation of **10** by formamide formation and the following $LiAlH_4$ reduction furnished *N*-methylated diamine **11** in 90% yield in two steps. Finally, acylation of the secondary amino group and treatment with methanolic HCl gave an enantiomerically pure HCl salt of **1**

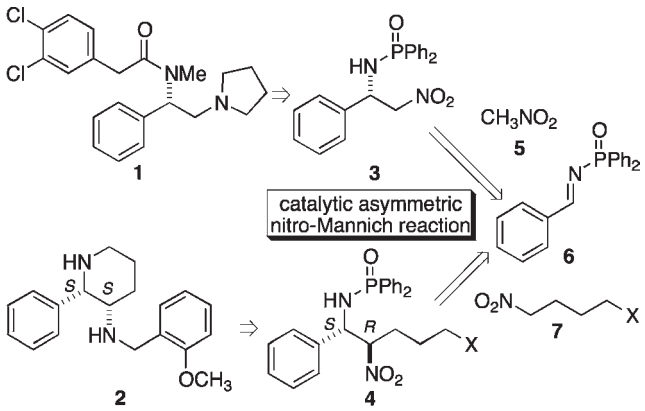
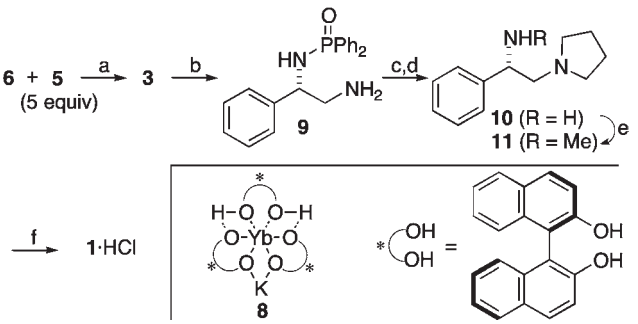


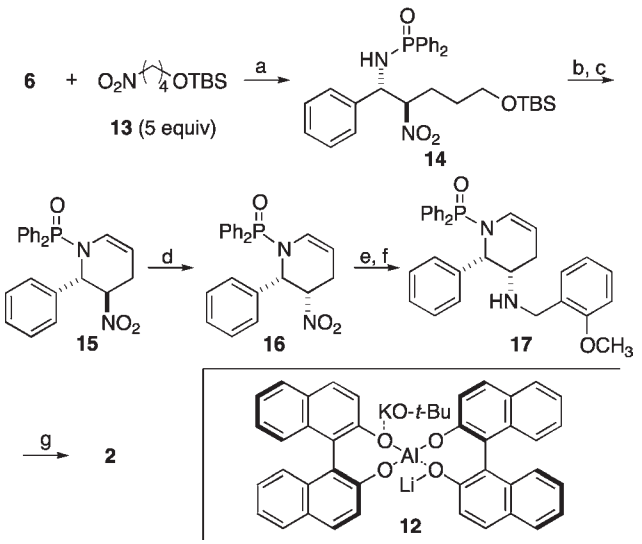
Figure 1.



Scheme 1. Reagents and conditions: a) i) **8** (20 mol%), toluene/THF (7 : 1), $-40\,^{\circ}$C, 79%, 91% ee; ii) recrystallization from MeOH, 78%, >99% ee; b) Raney-Ni, H_2, EtOH, rt, 92%; c) $OHC(CH_2)_2CHO$, $NaBH_3CN$, EtOH, p*H* 5, 0 °C, 81%; d) 1.5 M HCl-EtOH, rt, 98%; e) i) HCO_2Ac, $-20\,^{\circ}$C; ii)$LiAlH_4$, reflux, 90% from **10**; f) $ArCH_2COCl$, CH_2Cl_2, rt, 87%, Ar = 3,4-dichlorophenyl.

in 87% yield (35% overall yield), $[\alpha]_D^{25}$ $-105\,^{\circ}$ (*c* 1.1, $CHCl_3$); lit., $[\alpha]_D^{20}$ $-128\,^{\circ}$ (*c* 1.0, $CHCl_3$).[2b]

Scheme 2 shows the synthesis of **2**. For the first step, the second-generation ALB (ALB-II, **12**), prepared from AlLi[(*S*)-binaphthoxide]$_2$ and KO-*t*-Bu,[10] was used as a catalyst for the asymmetric nitro-Mannich reaction. The ALB-II is the catalyst of choice for nitroalkanes having a longer carbon chain, whereas the Yb catalyst is suitable for nitromethane.[6b] The reaction of **6** with nitroalkane **13** in the presence of (*S*)-ALB (20 mol%) and KO-*t*-Bu (18 mol%) at $-40\,^{\circ}$C provided nitroamine **14** as a mixture of diastereomers (*anti* : *syn* 6 : 1) in 90% yield with 77% ee (*anti*) after purification by column chromatography.[9,11] Chromatography-free purification of *anti*-**14** was also possible. After quenching the reaction, concentration of the crude mixture gave a precipitate, which was filtered off and washed with diethyl ether to afford crude crystal of almost diastereomerically pure *anti*-**14**. Eventually, recrystallization from MeOH produced *anti*-**14** with 97% ee in 40% yield (from **6**, two crops). Removal of the TBS group with HF/pyridine, Dess–Martin oxidation, and succeeding



Scheme 2. Reagents and conditions: a) **12** (20 mol%), CH_2Cl_2, −40 °C, 90%, dr 6 : 1, 77% ee (*anti*), [chromatography-free purification (see text): 97% ee, 40% from **6**]; b) HF-pyridine, THF, 0 °C to rt, quant; c) Dess-Martin periodinane, CH_2Cl_2, rt, 14 h, 86%; d) i) TMSCl, DBU, CH_2Cl_2, 0 °C, 1 h; ii) AcOH, −78 °C, 15 min, 83% from **15**; e) Zn, NH_4Cl, MeOH/H_2O, rt, 85%; f) *o*-anisaldehyde, $NaBH_3CN$, MS 3A, MeOH, rt, 3 h, 81%; g) $LiAlH_4$, THF, rt, 30%.

spontaneous cyclization furnished nitropiperideine **15** in 86% yield in three steps.[12] Desired epimerization of this cyclized product occurred via silyl nitronate to reverse the diastereomeric ratio to 1 : 5 in favor of the desired *syn*-form (**16**) in 83% yield. Epimerization on acyclic nitroamine **14** under the same conditions also reversed the diastereomeric ratio in 90% yield, albeit in a less satisfactory ratio (1 : 2). The nitro group of **16** was reduced to an amino group using Zn dust in 85% yield with negligible loss of stereochemical integrity.[13] The *o*-anisyl group was introduced by reductive alkylation to afford **17** in 81% yield. Treatment with $LiAlH_4$ induced cleavage of the diphenylphosphinoyl group and simultaneous reduction of the enamine moiety to yield **2** in 30% yield.[14] The optical purity of **2** was determined after transformation to its HCl salt by treating with methanolic HCl, $[\alpha]_D^{24} + 72^\circ$ (*c* 0.4, CH_3OH); lit., $[\alpha]_D + 77^\circ$ (*c* 1.0, CH_3OH).[3a]

In conclusion, we succeeded in synthesizing **1** and **2** using the catalytic asymmetric nitro-Mannich reactions as a key step, which enabled direct and stereoselective access to 1,2-diamines. Furthermore, selective acquisition of each diastereomer of a cyclic nitroamine was possible through epimerization, as demonstrated in the synthesis of **2**. To obtain the *syn*-isomer directly, *syn*-selective reaction is currently under investigation in this laboratory.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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7 $Yb(OiPr)_3$ was purchased from Kojundo Chemical Co., Ltd. (Fax: (+81)492-84-1351).

8 Procedure: The freshly prepared catalyst solution of **8** (0.025 M in toluene/THF 7/1, 2.0 mL, 0.20 mol equiv) (1 M = 1 mol dm^{-3}) was added to a test tube containing imine **6** (76 mg, 0.25 mmol), and the mixture was stirred for 10 min at room temperature. The mixture was cooled to −40 °C and stirred for 10 min before nitromethane (0.068 mL, 5.0 mol equiv) was added slowly over 27 h at the same temperature. After the addition of nitromethane was completed, the mixture was stirred for an additional 33 h at the same temperature, and then quenched by the addition of water (ca. 5 drops) and diluted with CH_2Cl_2 (ca. 5 mL). The mixture was allowed to warm up to room temperature, and after further dilution with CH_2Cl_2 (ca. 15 mL) the mixture was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, acetone/hexane 40/60 to 50/50) gave nitroamine **3** (72 mg, 79%) with 91% ee as an off-white solid.

9 The ee of **3** and *syn*-**14** was determined by HPLC analysis on a chiral stationary phase: for **3**, DAICEL Chiralcel OD; *i*PrOH/hexane 10/90; flow rate 1.0 mL min^{-1}; retention time 15 and 27 min, for the *syn*-**14**, DAICEL Chiralpak AD; *i*PrOH/hexane 10/90; flow rate 1.0 mL min^{-1}; retention time 9 and 26 min. The ee of *anti*-**14** was determined after transformation of the TBS group to Bn group as follows: i) HF-pyridine, THF, 0 °C to rt, ii) benzyl trichloroacetimidate, TFA, CH_2Cl_2, rt. HPLC analysis: DAICEL Chiralpak AD; *i*PrOH/hexane 10/90; flow rate 1.0 mL min^{-1}; retention time 35 and 52 min.

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11 Procedure: The 0.1 M solution of catalyst **12** (0.40 mL, 0.20 mol equiv) was added to a test tube containing imine **6** (61 mg, 0.20 mmol), and the mixture was stirred for 10 min at rt. The mixture was cooled to −40 °C and stirred for 10 min before a 1.0 M solution of KO-*t*-Bu in THF (0.036 mL, 0.18 mol equiv) and then nitroalkane **13** (0.25 ml, 5.0 mol equiv) were added at −40 °C. The mixture was stirred for 48 h at the same temperature, diluted with cold CH_2Cl_2 (−78 °C, ca. 5 mL) and then quenched by the addition of HOAc (ca. 6 drops). The mixture was transferred to a separatory funnel and diluted with additional CH_2Cl_2 (ca. 15 mL). The mixture was washed with H_2O, sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the resulting residue by column chromatography (SiO_2, CH_2Cl_2/acetone 19/1 to 9/1) gave nitroamine **14** (97 mg, 90%) as an off-white solid in a diastereomeric ratio of 6 : 1 (*anti* : *syn*) with 77% ee (*anti*) and 5% ee (*syn*).

12 When the alcohol moiety was converted to a leaving group such as iodide, methanesulfonate, or triflate in an attempt to construct piperidine ring by S_N2 type reaction, nucleophilic attack by the nitro group occurred exclusively, probably due to a reduced nucleophilicity of the amino group with an electron withdrawing substituent.

13 Other conditions such as SmI_2, Pd-C/H_2, $Pd(OH)_2/H_2$, Raney nickel/H_2, and $HCOONH_4$/Pd-C all gave rise to less satisfactory results because of epimerization, side reactions, and so on.

14 Spectroscopic data of the product obtained were identical with those reported in Ref. 3a.