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Synthesis of the Intermediate of Gemifloxacin by the Chemoselective Hydrogenation of 4-Cyano-3-methoxyimino-1-(*N-tert*-butoxycarbonyl)pyrrolidine. Part 2. The Palladium Catalysts in Acidic Media

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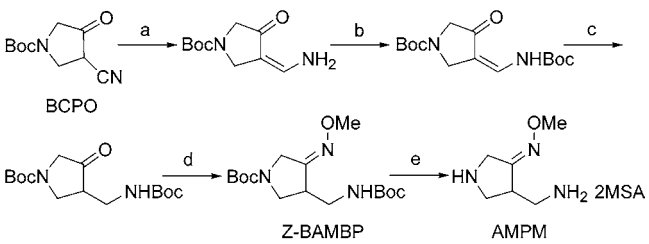
Abstract:

Chemoselective hydrogenation of 4-cyano-3-methoxyimino-1-(*N-tert*-butoxycarbonyl)pyrrolidine (CMBP) to 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulfonate (AMPM), the key intermediate for gemifloxacin, was investigated over Pd catalysts with in situ acid protection. Addition of more than 1.6 equiv of acidic protons for CMBP was found to drastically elevate both the reaction rate and selectivity to 4-aminomethyl-3-*Z*-methoxyimino-1-(*N-tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP) over Pd catalyst with a complete suppression of the major side reaction to 4-cyano-3-amino-1-(*N-tert*-butoxycarbonyl)-3,4-pyrroline (CABP). Methanol as the organic solvent was found to increase the hydrogenation rate greatly compared to other solvents with a negligible decrease of selectivity. The leaching of Pd by acid and consequent accumulation of Pd ion in the reaction mixture was negligible in CMBP hydrogenation. The novel process of chemoselective CMBP hydrogenation in acidic media over Pd catalyst was thus much simpler yet more efficient compared to the conventional one. The whole AMPM process time starting from 1-(*N-tert*-butoxycarbonyl)-4-cyanopyrrolidine-3-one (BCPO) could be reduced by at least approximately 15 h which would result in a great reduction of materials such as catalysts, (*t*-Boc)$_2$O, and solvent. Additionally, reduction of reaction steps improved the overall yield of AMPM significantly. Employment of methanesulfonic acid as an acidic agent in the hydrogenation step allowed an environmentally benign pathway to AMPM by omission of a neutralization step with an extra reduction in process time and materials consumed.

1. Introduction

4-Aminomethyl-3-*Z*-methoxyiminopyrrolidine (AMP) and 4-aminomethyl-3-*Z*-methoxyimino pyrrolidine methanesulfonate (AMPM) are novel compounds that are employed as intermediates in the synthesis of gemifloxacin (Factive), a novel quinolone antibacterial developed by LG Life Science Co. and approved by the U.S. Food and Drug Administration (FDA) in May 2003. It was found to possess extremely potent antibacterial activities against both Gram-negative and Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). Gemifloxacin showed an excellent in vitro and in vivo efficacy and good pharmacokinetic profile especially against respiratory tract infections that account for over 70% of all infections.[1−5]

Scheme 1. **Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidine methanesulfonate (AMPM) by conventional method[a]**



[a] Conditions: reagent: (a) Raney Ni, H_2, IPA−H_2O, 40 °C; (b) (*t*-Boc)$_2$O, KOH, DME−H_2O, 0 °C; (c) Pd/C, H_2, THF−H_2O, rt; (d) $MeONH_2$·HCl, NaOAc, EtOH−THF, 40 °C; (e) methanesulfonic acid, MeOH, 0 °C.[6,7]

AMPM is a key intermediate for the manufacture of gemifloxacin; in particular the methyloxime group in AMPM is known as the key group to represent the higher efficacy of gemifloxacin compared with other quinolone antibacterials.[2,5] The AMPM is at present produced from 1-(*N-tert*-butoxycarbonyl)-4-cyanopyrrolidine-3-one (BCPO) in a five-step process that comprises two hydrogenation steps and one protection step with (*t*-Boc)$_2$O (BOC) in the presence of a strong base (Scheme 1).[6,7] This current AMPM process has, however, some disadvantages; the process is rather complex, involving many reaction steps, and requires high skills in production. Many reaction steps with the high material cost make the process rather inefficient with substantial loss of products, and as a result, high production expenses are entailed in manufacturing AMPM.

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In an effort to reduce the number of reaction steps, we presented in a companion paper a novel AMPM process that consists of only three steps from BCPO.[8] The key reaction in this new process was chemoselective hydrogenation of 4-cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (CMBP) with in situ BOC protection preserving the methyloxime group which may also undergo hydrogenation. The process developed was far superior to the current five-step process, but further improvement was desired to be implemented in the practice because the chemoselective CMBP hydrogenation with in situ BOC protection gave only a moderate selectivity of ca. 70% to 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP) and a rather low hydrogenation rate. Over Raney cobalt and Ni-, Cr-doped Raney Co, the rate was low, and 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-(*N*-*tert*-butoxycarbonyl)amino-1-(*N*-*tert*-butoxycarbonyl)-pyrrolidine (BABABP) was formed as the main byproduct by hydrogenation of the methyloxime group as well as the cyano group in CMBP hydrogenation even in the presence of BOC. The Pd catalysts gave higher reaction rates than the doped Raney cobalt catalysts, but the selectivity to *Z*-BAMBP was a little lower. The major byproduct over Pd catalyst was CABP (4-cyano-3-amino-1-(*N*-*tert*-butoxycarbonyl)-3,4-pyrroline) which is formed by hydrogenolysis of the methyl group in the methyloxime group of CMBP and subsequent tautomerization of imine to enamine.

In this contribution we focus on Pd-catalyzed, liquid-phase CMBP hydrogenation with in situ acid protection in place of BOC. Under these conditions, we observed extensive leaching of metal by acid over Raney Co catalyst system without significant improvements in the reaction behavior. In fact, there are many reported cases where acids are employed as the reaction medium in nitrile hydrogenation over noble metal catalysts such as Pd and Pt.[9] It is known that acidic medium is highly effective in increasing the reaction rate by lowering the inhibition by the strong ligand function of the generated amine to the metal catalyst.[10] Substitution of BOC with acid also gives an economic benefit because BOC is expensive and somewhat troublesome to handle. However, there also exists a serious problem in the use of acidic medium, i.e. a neutralization process may be required that produces a huge amount of undesired salts to obtain nonprotonated amines as final products.[11] Noble metals may also be leached in acidic media that cause serious problems in the process. By using acid as an in situ protection agent, the AMPM process from BCPO may be simplified to a new three-step process as shown in Scheme 2. Furthermore, when MSA is employed as an in situ amine protection agent in CMBP hydrogenation, a further simplified process is obtained as shown in Scheme 3, as the obtained AMPM is of a methanesulfonic acid (MSA) salt form, the desired final product of the process.

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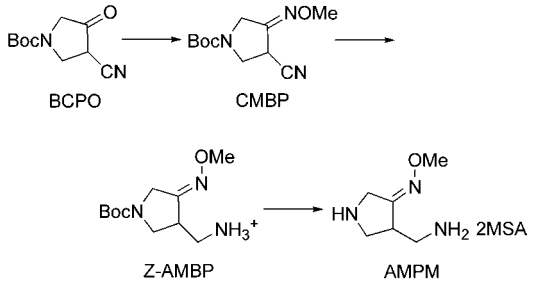
Scheme 2. **New process for manufacturing 4-aminomethyl-3-methoxyiminopyrrolidine methanesulfonate salt (AMPM) by chemoselective CMBP hydrogenation in acidic media**



Scheme 3. **New process for 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulfonate (AMPM) by chemoselective CMBP hydrogenation using MSA as acidic agent**

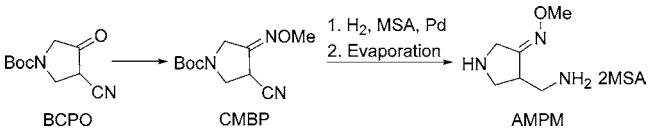


Table 1. **Operating conditions of HPLC**

column	symmetry C18, 5.0 um, 4.6 mm × 150 mm
mobile phase	A: acetonitrile (HPLC grade, Baker)
	B: water (0.1% trifluoroacetic acid)
total flow rate	1.0 mL/min
detection (UV)	197 nm
column temperature	ambient

Table 2. **Gradient elution composition of HPLC (A: acetonitrile, B: water (0.1% trifluoroacetic acid))**

time	% A	% B	time	% A	% B	time	% A	% B	time	% A	% B
0	20	80	5	70	30	13	100	0	21	20	80
3	50	50	11	100	0	19	100	0	24	20	80

Herein a dramatic acid effect in Pd-catalyzed chemoselective CMBP hydrogenation will be reported. In addition, the effect of water addition and the effect of MeOH as solvent will be presented. Anhydrous CMBP hydrogenation was also studied in acidic MeOH solvent over Pd catalyst, and the reaction pathway in this anhydrous condition will be discussed. Leaching of Pd catalyst by the acid may cause removal problems in the large-scale industrial application, and thus the leaching of Pd catalyst in CMBP hydrogenation was investigated as well.

2. Experimental Section

2.1. Analytical Methods. The reaction mixture was analyzed during the reaction using HPLC (Waters 1525) with a UV detector (Waters 2487). The operating conditions and gradient elution composition of HPLC are shown in Tables 1 and 2. Reaction products such as 4-aminomethyl-3-*Z*-methoxyimino 1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP), 4-cyano-3-amino-1-(*N*-*tert*-butoxycarbonyl)-(3,4)-pyrroline (CABP), 4-aminomethyl-3-amino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (AABP), 4-cyano-3-methoxyimino-pyrrolidine (CMP) and 4-aminomethyl-3-*Z*-methoxyimino-

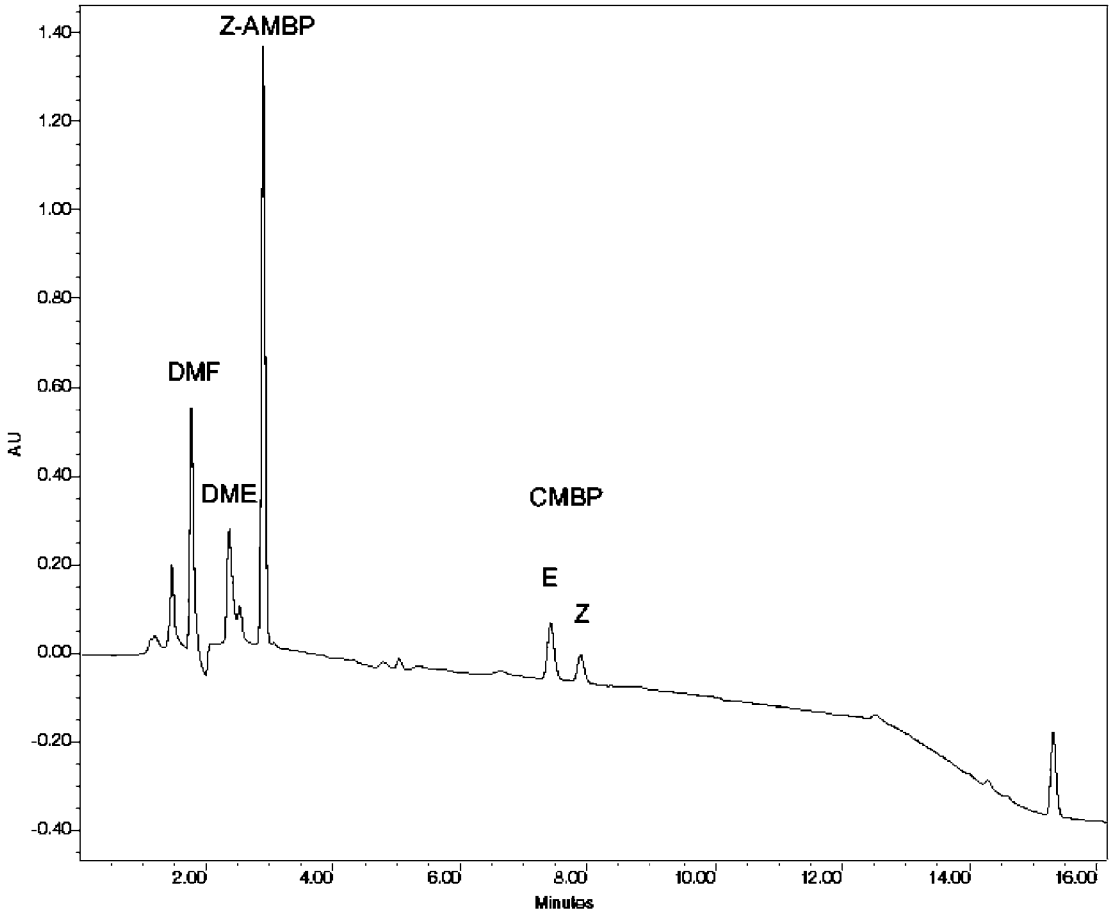


Figure 1. **Sample chromatogram in CMBP hydrogenation with in situ acid protection over Pd catalyst.**

Table 3. **List of the relative HPLC retention times for the compounds in the report**

compound	retention time [min]
AMPM	1.15
CMBP	*E*-isomer: 7.5, *Z*-isomer: 8.1
AABP	1.21
Z-AMBP	3.01
CABP	5.4
BCPO	4.37−6.33 (broad)
CMP	1.4
DME (dimethoxyethane)	2.4
DMF (dimethylformamide)	1.9

pyrrolidine methanesulfonate (AMPM) were identified by HPLC and LC−MS (Finnegan LCQ(067-MS-05)) by comparison with the standard samples obtained from the LG Life Science Co. Because only the *Z*-isomer of 4-aminomethyl-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (AMBP) is a desired product, the conversion and the selectivity to *Z*-AMBP were calculated on the basis of the amount of *Z*-isomers. A list of the relative HPLC retention times for the compounds in the report is presented in Table 3 and a sample chromatogram included in Figure 1.

2.2. Preparation of 4-Cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (CMBP). The preparation procedure of CMBP is described in detail in the accompanying paper.[8]

2.3. Catalysts. The supported Pd catalysts and other noble metal catalysts such as Pt, Ru, and Rh as well as their precursors were purchased from Aldrich. Most of the Pd catalysts were used as received, but if necessary they were utilized after reduction in H_2 stream at 473 K for 1−2 h. Supported Pt, Ru, and Rh catalysts were activated in H_2 stream at 473−773 K before hydrogenation.

Some Pd/alumina catalysts were manufactured in the laboratory and utilized for CMBP hydrogenation. A calculated amount of $PdCl_2$ was dissolved in aqueous HCl solution (pH ≅ 2) and Al_2O_3 (Aldrich) powders were introduced into the solution. The mixture was vigorously stirred for 1−2 h to obtain the Pd^{2+}-adsorbed alumina. Upon removal of H_2O in vacuo, Pd^{2+}/alumina was obtained. These materials were utilized in CMBP hydrogenation directly.

2.4. **Liquid-Phase Hydrogenation of CMBP To Prepare 4-Aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP).** The liquid-phase hydrogenation of CMBP was conducted in the 100-mL Hastelloy-C autoclave reactor (Autoclave Engineers). Typically 0.5 mmol CMBP (0.12 g), *x* mL of organic solvent, (50 − *x*) mL of water, 0.1−20 mol % metallic content with respect to CMBP with/without support as catalyst and additives (e.g., acid) were introduced into the reactor. After purging the reactor twice with hydrogen, the reactor was pressurized to 60−500 psi with H_2. The reaction was conducted typically at 298−323 K with agitation at 1000 rpm to minimize the

external mass transfer limitation. After CMBP hydrogenation, the mixture was filtered, and the filtrate was evaporated in vacuo below 313 K to remove organic solvent. The isolated solution was shaken with methylene chloride, and the organic phase was discarded. To obtain the nonprotonated *Z*-AMBP, the aqueous phase was neutralized with a saturated $NaHCO_3$ solution and extracted with methylene chloride. By the removal of CH_2Cl_2 in vacuo, yellowish, oily nonprotonated *Z*-AMBP could be obtained.

Spectral data for *Z*-AMBP: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (2H, broad, s), 3.89 (3H, s), 3.87 (1H, broad, s), 3.77 (1H, broad, m), 3.36 (1H, broad, s), 2.89 (2H, broad, s), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 151.0, 76.6, 58.7, 45.1, 44.5, 42.9, 40.8, 25.0; IR 1694.5 cm $^{-1}$.

2.5. Preparation of 4-Aminomethyl-3-*Z*-methoxyimino-pyrrolidine Methanesulfonate (AMPM). As methanesulfonic acid (MSA) was used as the acidic agent in CMBP hydrogenation, AMPM could be produced from *Z*-AMBP without a neutralization step. After CMBP hydrogenation, the mixture was filtered, and the filtrate was evaporated in vacuo below 313 K to remove organic solvent. The isolated solution was shaken with methylene chloride, and the organic phase was discarded. The obtained aqueous phase was evaporated again in vacuo below 313 K to remove water completely. *Z*-AMBP was converted to AMPM, and the concentrate of AMPM was dissolved in methanol in a ratio of 1 g of AMPM/5 mL of MeOH. The solution was chilled below 273 K, and the seed was introduced thereto. The mixture was stirred at 263 K for 2 h to give white crystals of AMPM which were collected and dried under vacuo at 273 K.

Spectral data for AMPM: ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.25 (2H, broad, $>NH_2^+$), 7.95 (3H, broad, $-NH_3^+$), 3.96 (2H, dd, J = 40 Hz, 17.2 Hz), 3.86 (1H, s), 3.68 (1H, m), 3.26 (2H, m), 3.10 (1H, ddd, J = 32 Hz, 7.8 Hz, 4 Hz); IR spectrum 1638.4, 1598.5 cm $^{-1}$.

2.6. Leaching of Pd. Acidic solution was prepared by addition of 6.3 mL of MSA to 120 mL of MeOH + 30 mL of water mixture and 0.6 g of 10 wt % Pd/C was introduced thereto. This suspension was shaken and divided into three batches; the first batch was filtrated right away to give the solution that represents the initial amount of Pd ions in the Pd/C introduced. The second batch was stirred at 298 K in ambient air for 2 h, the standard reaction time of CMBP hydrogenation. Five grams of CMBP was introduced to the last batch, and the mixture was subjected to hydrogenation with stirring for 2 h at the same temperature and pressure as employed for CMBP hydrogenation. After filtration, the concentration of Pd ions was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) using SPECTRO, flame modular EOP at 360.955 nm. Before measurement, C−HNO_3 was added to the liquid samples, and solvents were evaporated. The product was dissolved in aqueous HCl and analyzed. The operating conditions of the instrument are shown in Table 4.

3. Results and Discussion

3.1. Pd Precursors as Catalysts. At first, various Pd(II) precursors were employed as catalysts for CMBP hydrogenation without the extra addition of acid. $Pd(OAc)_2$, $PdCl_2$, and $Pd(NO_3)_2$ showed the catalytic activity to yield *Z*-AMBP with coproduction of 4-cyano-3-amino-1-(*N*-*tert*-butoxycarbonyl)-3,4-pyrroline (CABP) while $Pd(C_6H_5CN)_2Cl_2$ and $Pd(NH_3)_4Cl_2$ showed no activity at all (Table 5). The catalysis by those Pd precursors may be originated from Pd(0) by reduction of the Pd(II) ion with hydrogen.

Table 4. **ICP-AES operating parameters used for Pd determination**

instrument	SPECTRO, flame modular EOP
plasma power	1200 W
coolant gas flow	12.0 L/min
auxiliary gas flow	1.0 L/min
nebulizer gas flow	0.85 L/min
nebulizer	Spectro, cross-flow type
sample uptake	1.2 mL/min

Table 5. **Liquid-phase CMBP hydrogenation over Pd catalyst system: effect of Pd precursors as catalyst[a]**

precursor	time [h]	conv of *Z*-CMBP [%]	selectivity [%]		
			Z-AMBP	CABP	AABP
$Pd(OAc)_2$	1	10	76	20	1
	7	21	68	25	4
$Pd(C_6H_5CN)_2Cl_2$	1	0	–	–	–
	7	0	–	–	–
$PdCl_2$	1	12	73	21	1
	7	23	66	25	4
$PdCl_2$[b]	1	41	84	10	1
	7	64	77	15	2
$Pd(NH_3)_4Cl_2$	1	0	–	–	–
	7	0	–	–	–
$Pd(NO_3)_2$	1	14	72	21	1
	7	28	65	26	4

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; IPA 30 mL; H_2O 20 mL; Pd 5 mol % of CMBP, H_2 500 psi; T = 298 K. [b] Pd 20 mol % of CMBP.

All active and selective Pd precursors in Table 5 contained anions that would make the solution acidic. Furthermore, we observed that the higher loading of $PdCl_2$ brought a higher selectivity to *Z*-AMBP with a decline of the selectivity to CABP as well as a higher reaction rate. The increase of the hydrogenation rate was easily understood with the increase of the amount of $PdCl_2$. However, the increase of the selectivity to *Z*-AMBP was unexpected. The increase of the amount of $PdCl_2$ would result in a lower pH of reaction medium by HCl liberated by reduction of $PdCl_2$ by H_2. This observation of the high selectivity to *Z*-AMBP at low pH eventually led us to the discovery described in this contribution regarding the highly chemoselective hydrogenation of CMBP over Pd catalysts in acidic media.

3.2. Effect of Acidity of Reaction Medium.[13] To confirm the favorable effect of acidity, aqueous HCl was introduced in the reaction mixture containing $PdCl_2$. With [HCl]/

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(13) The conversion of *E*-isomer of CMBP was considerably slower than that of *Z*-isomer, and the selectivity to *E*-AMBP was around 60% in this Pd/acid catalytic system.

Table 6. **Liquid-phase CMBP hydrogenation over Pd catalyst system: effect of solvent and acidity[a]**

organic solvent	[HCl]/[CMBP]	conv of *Z*-CMBP [%]	selectivity [%]		
			Z-AMBP	CABP	AABP
IPA	0	12	71	22	2
IPA	2	98	92	0	1
IPA[b]	0	13	75	19	2
IPA[b,c]	2	100	92	0	1
EtOH	2	99	92	0	1
THF	2	94	93	0	1
DME	2	93	95	0	1

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; organic solvent 30 mL; H_2O 20 mL; $PdCl_2$ 5mol % for CMBP; H_2 500 psi; $T = 298$ K; time = 1.5 h. [b] $Pd(NO_3)_2$ was used as catalyst in place of $PdCl_2$. [c] HNO_3 in place of HCl.

[CMBP] = 2, both the reaction rate and the selectivity to *Z*-AMBP increased drastically with total suppression of the side reaction to CABP (Table 6). $Pd(NO_3)_2/HNO_3$ system was also found to increase the rate and the selectivity dramatically. It was therefore conjectured that these dramatic improvements of the CMBP hydrogenation in the presence of acid were owing to the acidic proton. With DME as the organic solvent, the selectivity was as high as 95% with only traces of AABP and other unidentified byproducts, although the rate was slightly lower than those for other solvents tested.

The effects of [HCl]/[CMBP] ratio (*R*) are shown in Figure 2. Both the CMBP conversion and the selectivity to *Z*-AMBP increased dramatically as *R* increased from 0 to 2 with suppression of the side reaction to CABP. Both the hydrogenation rate and the selectivity to *Z*-AMBP reached the maximum point at $R \cong 1.6$, and a further increase in the amount of HCl did not affect the reaction behavior significantly. When *R* was about 10 or even higher, the selectivity decreased slightly. The decline of the selectivity at the high ratios is possibly due to the decomposition of the CMBP by HCl. Indeed, the decomposition of CMBP in strong acidic media at pH = 1 without hydrogen was observed to some extent. Therefore, the appropriate amount of HCl around the ratio of $R = 1.6$ or keeping the pH of the reaction mixture around 2 are expected to be advantageous to attain high yields of *Z*-AMBP with minimal decomposition of CMBP by the acid.

3.3. Supported Catalysts in Acidic Media. Supported catalysts have many advantages for industrial practice such as convenience of separation and recovery of catalyst relative to homogeneous catalysts and high catalytic activity due to the high dispersion of the metallic component on the support compared to unsupported catalysts. Here the applicability of acid to the supported Pd catalyst system was investigated, with the results summarized in Table 7. As in the unsupported Pd precursor system, supported Pd catalysts also showed a dramatic increase both in the CMBP conversion and the selectivity to *Z*-AMBP in acidic media. Pd/C showed a higher hydrogenation rate than Pd/Al_2O_3 with slightly lower selectivity to *Z*-AMBP. A 1% Pd/alumina catalyst made in the laboratory by adsorption of $PdCl_2$ onto Al_2O_3 also showed a good performance.

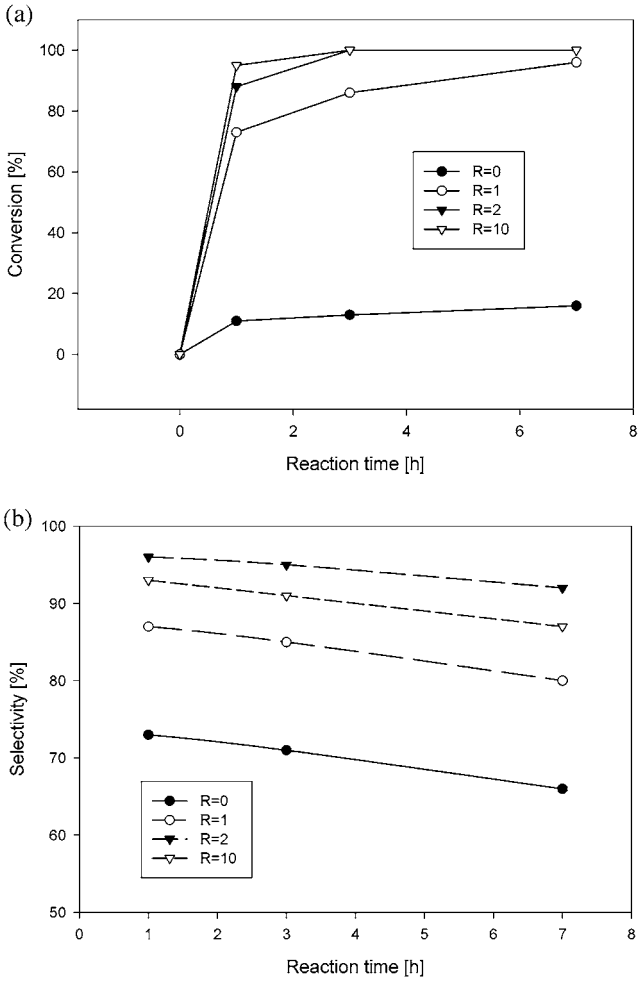


Figure 2. **Effects of *R* ([HCl]/[CMBP]) on (a) the *Z*-CMBP conversion and (b) the selectivity to *Z*-AMBP in liquid-phase hydrogenation with $PdCl_2$: CMBP 0.5 mmol; DME 30 mL; H_2O 20 mL; $PdCl_2$ 5mol % of CMBP; H_2 500 psi, $T = 298$ K.**

Table 7. **Liquid-phase CMBP hydrogenation over Pd catalyst system: supported Pd catalyst in acidic media[a]**

catalyst	acid	time [h]	conv of *Z*-CMBP [%]	selectivity [%]		
				Z-AMBP	CABP	AABP
5% Pd/Al_2O_3	HCl	1	87	96	0	1
		2	100	95	0	1
5% Pd/C	HCl	1	96	95	0	1
		2	100	93	0	1
1% Pd/Al_2O_3[b]	HCl	1	87	96	0	0
		2	100	95	0	1
5% Pd/Al_2O_3	HNO_3	1	88	96	0	0
		2	100	95	0	1
5% Pd/Al_2O_3[c]	AcOH	1	91	97	0	0
		2	100	95	0	1
5% Pd/Al_2O_3	MSA	1	86	96	0	0
		2	100	95	0	1

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; DME 30 mL; H_2O 20 mL; Pd 5 mol % for CMBP; H_2 500 psi; $T = 298$ K; [Acid]/[CMBP] = 2. [b] Prepared by adsorption of $PdCl_2$ at pH = 2 with aqueous HCl onto the Al_2O_3 and subsequent evaporation of water in vacuo. [c] AcOH 30 mL as acidic agent in place of DME, pH = 1.5.

Other acids such as acetic acid and methanesulfonic acid (MSA) also showed a similar improvement (Table 7). Using MSA as the acidic agent in CMBP hydrogenation is

Table 8. **Liquid-phase CMBP hydrogenation in HCl medium over other noble metal catalysts[a]**

catalyst	conversion of *Z*-CMBP [%]	selectivity to *Z*-AMBP [%]
1 wt % Pt/C	15	83
PtO_2	19	80
5 wt % Ru/Al_2O_3	9	85
5 wt % Ru/C	13	83
5 wt % Rh/Al_2O_3	22	75

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; DME 30 mL; H_2O 20 mL; metal component 5 mol % of CMBP; H_2 500 psi; $T = 298$ K; [HCl]/[CMBP] = 2; time = 24 h; supported metal catalysts were prereduced at 523 K for 3 h in H_2 stream.

particularly beneficial in that the final product in the AMPM process is of a MSA salt form, and thus the process can be further simplified by omission of the neutralization step. If other acids such as HCl were used, neutralization of acidic *Z*-AMBP salt would be required prior to the deprotection with MSA to manufacture AMPM. Neutralization is actually an industrially unwelcome process that yields massive amounts of undesired salts that are environmentally unacceptable. In Scheme 3 a further simplified AMPM process by using MSA as the acidic agent is presented. The MSA salt of *Z*-AMBP produced after hydrogenation can be transformed into AMPM by the simple removal of water in vacuo together with deprotection of the Boc group in *Z*-AMBP. This new CMBP hydrogenation method over a Pd/acid catalytic system is a versatile one, as other acidic salts of AMP such as AMP−HCl salt can also be easily produced in a similar way with corresponding acid in CMBP hydrogenation.

The effects of H_2 pressure and reaction temperature were investigated in acidic media over Pd catalyst. Variation in H_2 pressure did not affect the selectivity to *Z*-AMBP significantly, while the rate decreased slightly as the pressure decreased. As the reaction temperature increased, the rate was elevated while the selectivity decreased a little. Other noble metal catalysts (Pt, Ru, and Rh) were also tested for CMBP hydrogenation with an acidic agent, and the results are shown in Table 8. In comparison with the Pd catalysts, the hydrogenation activities over those catalysts were lower.

Thus, the addition of an acid in chemoselective CMBP hydrogenation over metal catalysts brings a dramatic improvement in *Z*-AMBP yield. The acid appears to play two key roles: (i) in situ protection of amine produced to prevent the side reaction of *Z*-AMBP to AABP or to higher amines and (ii) to increase the hydrogenation activity and selectivity to *Z*-AMBP by suppressing the side reaction to CABP. In nitrile hydrogenation over noble metal catalysts such as Pd and Pt, the generated amine is known to reduce the reaction rate by strong ligation to the metal catalysts. Addition of acid alleviates this inhibitory effect of the generated amine by protonating the amine.[10] The remarkable increase in the selectivity by suppressing the side reaction of methyloxime hydrogenation to CABP in the presence of acid was a pleasant surprise for us although its mechanism is unclear at the present stage.

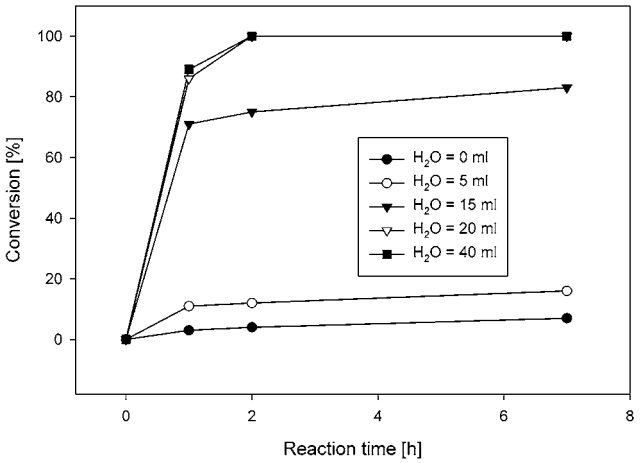


Figure 3. **Influence of amount of H_2O in the liquid-phase CMBP hydrogenation over 5% Pd/Al_2O_3: CMBP 0.5 mmol; H_2O + DME = 50 mL; Pd 5 mol % of CMBP as 5% Pd/Al_2O_3; H_2 500 psi; $T = 298$ K; [HCl]/[CMBP] = 2.**

3.4. Effects of the Amount of Water. As shown in Figure 3, the amount of water in the solvent was varied. At the anhydrous condition, the rate of CMBP conversion was very low, and the conversion increased very little with time. This is in accord with general observations reported in the literature.[11] As the content of water in the solvent increased up to 0.3 (15 mL), the rate also increased. Yet, the reaction stopped before complete conversion of CMBP was reached. At a ratio above 0.4 (20 mL), the rate became faster, and complete conversion was obtained. With a change in the amount of water, the variation of selectivity to *Z*-AMBP was almost negligible. There seem to be no significant side reactions caused by water either, such as the hydrolysis of imines.[9,12]

Although the reason for the promotional effect of water is not clear at present, one might suspect that the acid could not sufficiently protonate the *Z*-AMBP produced at low water concentrations. As mentioned earlier, the produced amine acts as an inhibitor to the catalyst, and addition of acid is effective in increasing the rate of nitrile hydrogenation, owing to the protonation of the amine to an ammonium ion and thus suppressing the poisoning effect of the amine. Therefore, it seems that water affects this protonation of the amine and should be present in a sufficient amount to be effective.

3.5. Further Optimization for Industrial Applications. So far our experiments on CMBP hydrogenation were carried out for too dilute a substrate concentration of ca. 0.002 g/mL solvent. For an industrial application of the process, the concentration should be about 0.2−0.05 g of substrate per milliliter. It is also desired that the amount of Pd catalyst be reduced to below 1 wt % metal content relative to the substrate and hydrogen pressure greatly reduced from 500 psi.

In Table 9, the concentration of substrate and the amount of catalyst were varied. When the substrate concentration was increased 25 times, the conversion of *Z*-CMBP was reduced from 96% to 64%. When the catalyst concentration was reduced from 2.5 to 0.5 wt % of the substrate, an excessively prolonged reaction time of 24 h was needed to obtain 89% *Z*-CMBP conversion. When MeOH was utilized

Table 9. **Liquid phase CMBP hydrogenation over Pd catalyst system: Effects of substrate concentration and the effect of MeOH[a]**

organic solvent	g/mL substrate	wt% Pd relative to substrate	conversion of *Z*-CMBP [%]	selectivity to *Z*-AMBP[%]
DME	0.002	2.5	96	94
DME	0.05	2.5	64	95
DME[b]	0.05	0.5	89	92
MeOH	0.002	0.5	100	93
MeOH	0.05	0.5	100	92
MeOH[c]	0.1	0.5	100	91
MeOH[c,d]	0.1	0.5	76	94

[a] The following reaction conditions were used unless otherwise stated. Organic solvent 30 mL; H_2O 20 mL; 10 wt % Pd/C; H_2 500 psi; $T = 298$ K; [MSA]/[CMBP] = 2; time = 1 h. [b] Time = 24 h. [c] H_2 100 psi. [d] 10 wt % Pd/alumina (Aldrich).

Table 10. **Liquid-phase anhydrous CMBP or CMP hydrogenation in MeOH over Pd catalyst[a]**

substrate	g/mL substrate	conversion to *Z*-form[%]	selectivity to *Z*-form [%]
CMBP	0.1	83	85[b]
CMP	0.002	100	76[c]
CMBP	0.002	91	93[b]
CMBP[d]	0.002	trace	−

[a] The following reaction conditions were used unless otherwise stated. MeOH 50 mL; 0.5 wt % Pd for substrate as 10 wt % Pd/C; H_2 500 psi; $T = 298$ K; [MSA]/[CMBP] = 2; Time = 1 h. [b] Selectivity to AMPM + Z-AMBP. [c] Selectivity to AMPM. [d] [MSA] = 0.

as an organic solvent, a dramatic enhancement of the hydrogenation rate was observed. Hydrogenation of CMBP was accelerated about 6−7 times in MeOH solvent compared to that in DME solvent, with a negligible decrease of the selectivity to *Z*-AMBP. By using MeOH as the organicsolvent, satisfactory reaction performance (100% *Z*-CMBP conversion and 91% *Z*-AMBP selectivity) was achieved at industrially favored conditions of the substrate concentration 0.1 g/mL, Pd content 0.5 wt % of the substrate, and H_2 pressure of 100 psi, as shown in Table 9.

The reaction rate with MeOH as the solvent was so high that the CMBP hydrogenation also proceeded in anhydrous MeOH solvent. Other solvents such as DME, EtOH, IPA, and THF showed reasonable activity only when a certain amount of water was introduced, as described earlier. The CMBP hydrogenation was studied in anhydrous MeOH solvent, and the results are shown in Table 10. The lower reaction rate and lower selectivity to *Z*-AMBP and AMPM were observed without water. To identify the cause of the decrease of the selectivity, 4-cyano-3-methoxyiminopyrrolidine (CMP) hydrogenation in anhydrous MeOH was carried out. CMP was manufactured easily by deprotection of the Boc group in CMBP with MSA. In CMP hydrogenation, a significantly lower AMPM selectivity was observed with formation of several new side products in comparison with CMBP hydrogenation. Thus, at the anhydrous condition, deprotection of the Boc group in CMBP seems favored to give CMP which is subsequently hydrogenated to AMPM with a reduced selectivity. This pathway takes place in competition with the hydrogenation of CMBP to *Z*-AMBP

Scheme 4. **CMBP hydrogenation pathway to AMPM over Pd catalyst in an anhydrous acidic MeOH medium via two parallel paths: (a) through deprotection of BOC in CMBP by MSA and (b) through hydrogenation of cyano group**

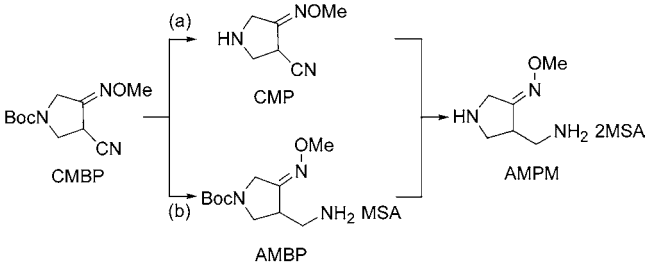


Table 11. **Pd ion concentration after leaching Pd/C in acidic medium[a]**

conditions	mg/L Pd ion	mg Pd ion in 50 mL soln	% Pd ion against Pd introduced
initial	0.978	0.049	0.245
under ambient air for 2 h	1.828	0.091	0.455
under 100 psi H_2 for 2 h	0.08	0.004	0.021

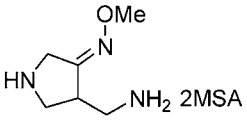
[a] Experimental conditions: acidic media = 40 mL MeOH + 10 mL H_2O + 2.1 mL MSA. Catalyst = 10 wt % Pd/C 0.2 g (20 mg Pd). $T = 298$ K.

and subsequent deprotection of *Z*-AMBP to AMPM as depicted in Scheme 4. Anhydrous CMBP hydrogenation through path b with minimization of deprotection of the Boc group in CMBP (path a) could be practiced by reducing the CMBP concentration and, accordingly, the amount of MSA (Table 10) or increasing the catalyst/substrate ratio. In this case, the selectivity was as high as the case where water was added while the rate was reduced by about 50% compared with that in aqueous CMBP hydrogenation. Hence, the proper addition of water was found to be beneficial for a high reaction rate and a high AMPM selectivity even with MeOH as the solvent. The reaction did not proceed without MSA under this condition.

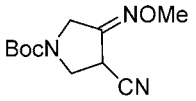
3.6. Leaching of Pd Metal by Acid. When metallic catalysts are employed with acidic media, leaching of the metallic component by acid and dissolution of metal ions in the reaction medium is always a concern. The leaching is quite troublesome because it may cause deactivation of the catalyst and contamination of the product. In practice, this may require makeup of catalysts and separation of metal ions from the reaction medium.

Leaching of Pd metal by acid in air and in hydrogen atmosphere at the same conditions as CMBP hydrogenation was investigated, as shown in Table 11. The procedure for this experiment is given in the Experimental Section. The concentration of Pd ions in the first batch was 0.978 mg/L, which corresponds to about 0.25% of the total amount of Pd introduced. This corresponds to the amount of Pd that is formed immediately upon contact between Pd/C and the acidic medium. The concentration of Pd ions in the second batch was 1.828 mg/L or 0.455% of the total Pd introduced, indicating additional leaching in the acidic media (pH = 1.5) for 2 h under ambient air. By contrast, the concentration of Pd ions in the third batch was decreased to 0.08 mg/L or

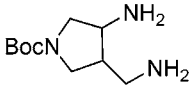
Scheme 5. **Glossary**



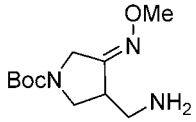
: 4-aminomethyl-3-Z-methoxyiminopyrrolidine methanesulfonate (AMPM)



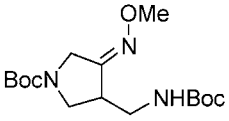
: 4-cyano-3-methoxyimino-1-(N-t-butoxycarbonyl)-pyrrolidine (CMBP)



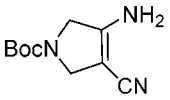
:4-aminomethyl-3-amino-1-(N-t-butoxycarbonyl)-pyrrolidine (AABP)



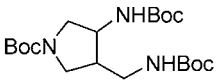
:4-aminomethyl-3-Z-methoxyimino 1-(N-t-butoxycarbonyl)-pyrrolidine (Z-AMBP)



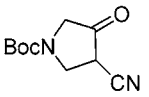
:4-(N-t-butoxycarbonyl)-aminomethyl-3-Z-methoxyimino-1-(N-t-butoxycarbonyl)-pyrrolidine (Z-BAMBP)



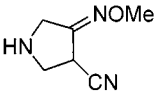
: 4-cyano-3-amino-1-(N-t-butoxycarbonyl)-(3,4)-pyrroline (CABP)



:4-(N-t-butoxycarbonyl)-aminomethyl-3-(N-t-butoxycarbonyl)-amino-1-(N-t-butoxy-carbonyl)- pyrrolidine (BABABP)



:1-(N-t-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO)



:4-cyano-3-methoxyiminopyrrolidine (CMP)

0.02% of the total amount of Pd introduced for 2 h under hydrogenation reaction conditions. This result shows that Pd ions initially present in the Pd/C are reduced to the metallic phase by hydrogen during CMBP hydrogenation and that further accumulation of Pd ions by leaching does not take place in this case. Thus, the highly reducing atmosphere of CMBP hydrogenation suppresses leaching of Pd from Pd/C by the acidic medium to less than 0.1 ppm level.

4. Conclusions

Addition of more than 1.6 equiv of acidic protons for CMBP was found to drastically improve both the reaction rate and selectivity to *Z*-AMBP over Pd catalyst with suppression of the side reaction to CABP in CMBP hydrogenation. MeOH as the organic solvent was found to increase the hydrogenation rate compared to other solvents with a negligible decrease of selectivity. The leaching of Pd by acid and consequent accumulation of Pd ions in the reaction mixture were negligible in CMBP hydrogenation. The novel process of chemoselective CMBP hydrogenation in acidic media over Pd catalyst (Scheme 3) was thus much simpler yet more efficient compared to the conventional one (Scheme 1). The whole AMPM process time starting from BCPO could be reduced by at least approximately 15 h with a great reduction of materials such as catalysts, BOC, and solvent. Additionally, a decrease in reaction steps improved the overall yield of AMPM significantly. Employment of MSA as an acidic agent in the hydrogenation step allowed an environmentally benign pathway to AMPM by omission of the neutralization step with extra reduction in process time and materials consumed.

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