# Synthesis of Primary Aromatic Amides by Aminocarbonylation of Aryl Halides Using Formamide as an Ammonia Synthon

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Primary aromatic amides were prepared by a palladium-catalyzed aminocarbonylation reaction of aryl halides in high yields (70-90%) using formamide as the amine source. The reactions require a palladium catalyst in combination with a nucleophilic Lewis base such as imidazole or 4-(dimethylamino)pyridine (DMAP). Aryl, heteroaryl, and vinyl bromides and chlorides were converted to the primary amides under mild conditions (5 bar, 120 °C) using 1 mol % of a palladiumphosphine complex. Best results were obtained in dioxane using triphenylphosphine as the ligand and DMAP as the base. For activated aryl bromides, a phosphine-to-palladium ratio of 2:1 was sufficient, but less reactive aryl bromides or aryl chlorides required ligand-to-palladium ratios up to 8:1 in order to stabilize the catalyst and achieve full conversion. The influence of catalyst, base, solvent, pressure, and temperature was studied in detail. The mechanism of the reaction could be clarified by isolating and identifying the reaction intermediates. In addition, methylamides and dimethylamides were prepared by the same method using N-methylformamide and N,N-dimethylformamide as the amine source.

## Introduction

The palladium-catalyzed aminocarbonylation is an important method for the selective and direct synthesis of aromatic amides starting from aryl halides, and the reactions of primary and secondary amines to the corresponding secondary and tertiary amides are well documented (eq 1). $^{1,2}$ 



In contrast to this, only a few publications describe the direct synthesis of primary amides by carbonylation of aryl halides ( $\mathbb{R}^1$ ,  $\mathbb{R}^2 = H$ ). Morera and Ortar<sup>3</sup> reacted aryl and vinyl iodides and triflates with hexadimethylsilazane (HMDS) as an ammonia synthon. The silyl-protected amides initially formed in the carbonylation reaction were hydrolyzed during the acidic workup, and the primary amides were obtained in good to excellent yields.

Drawbacks of the method are the price of HMDS and the low atom efficiency: less than 10 wt % of HMDS ended up in the product. Ueda et al.<sup>4</sup> used a titanium-nitrogen compound as an ammonia source, giving the primary amide in modest yields. Interestingly, the titaniumnitrogen complex was prepared by fixation of elementary N<sub>2</sub> with in situ prepared activated titanium species (Li/ Ti(OiPr)<sub>4</sub>/TMSCl). As stated in both publications, the direct use of ammonia in the aminocarbonylation of aryl halides did not give satisfactory results, and it was speculated that ammonia is not sufficiently nucleophilic. On the other hand, Martinelli and Vries<sup>5</sup> reported the aminocarbonylation of an aryl iodide with ammonia in excellent yield but no details were given. A drawback is the handling of gaseous ammonia, which is inconvenient on a small scale. In all three procedures the major difficulties are connected with the source of the ammonia. A simple and general procedure for the aminocarbonylation to primary amides using a cheap and easy to handle ammonia source would obviously be of great interest to synthetic chemists.



The starting point of our investigation was the observation of dimethylamide 3 as a side product in the

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 Table 1. Effect of Ligand Types, Temperature, and

 Pressure on the Carbonylation of 1 in Formamide<sup>a</sup>

entry	ligand <sup>b</sup>	temp (°C)	CO pressure (bar) <sup>c</sup>	conv of <b>1</b> (%)	yield of <b>4</b> (%) <sup>d</sup>
1	dppf	120	5	100	38
2	dpephos	120	5	100	56
3	dppb	120	5	100	79
4	binap	120	5	100	85
5	$PPh_3$	120	5	100	96
6	$PPh_3^e$	120	5	100	82
7	$PPh_3$	25	5	0	0
8	$PPh_3$	90	5	100	97
9	$PPh_3$	150	5	100	74
10	PPh <sub>3</sub>	120	1	100	90
11	PPh <sub>3</sub>	120	8	100	92
12	PPh <sub>3</sub>	120	50	100	93

<sup>*a*</sup> Reaction conditions: **1** (35.6 mmol), imidazole (38 mmol), PdCl<sub>2</sub> (0.36 mmol), and ligand (Pd/P = 1:4) in 25 mL of formamide, in a 250 mL glass autoclave at the indicated temperature for 18 h. <sup>*b*</sup> dppf: 1,1'-bis(diphenylphosphino)ferrocene, dpephos: 2,2'-bis-(diphenylphosphino)diphenyl ether, dppb: 1,4-bis(diphenylphosphino)butane, binap: (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, PPh<sub>3</sub>: triphenylphosphine. <sup>*c*</sup> Initial pressure at room temperature. <sup>*d*</sup> GC yields. <sup>*e*</sup> Pd/P = 1:2.

reductive carbonylation of 3-bromobenzotrifluoride (1) in DMF (eq 2). Similar observations were reported by other groups, and the formation of the dimethylamide was ascribed to the reaction of an aroyl palladium species with the solvent.<sup>3.6</sup> We recognized this reaction as a valuable method for the preparation of various amides, since formamides would be cheap and easy to handle amine sources, and of special interest was the synthesis of primary amides using formamide. Herein we report the development of this novel amidocarbonylation reaction for the efficient preparation of primary amides. The critical reaction parameters and the scope of the methodology were evaluated.

#### Results

The aryl bromide **1** was used as a weakly activated substrate to investigate the carbonylation reaction with DMF (eq 2). With bases such as tributylamine, DBU, or DABCO, the dimethylamide **3** was formed in very low yields (<4%). However, with imidazole as the base, amide **3** was isolated in 78% yield. Performing the same reaction in formamide instead of DMF afforded the primary amide **4** in similar yield (75%) (eq 3).



The influence of critical reaction parameters (temperature, CO pressure, ligand type) was investigated for the reaction of **1** with formamide (Table 1). In all experiments, full conversion of the starting material **1** was observed, except when the reaction was carried out at room temperature (entry 7). The highest yields of **4** were obtained at temperatures between 90 and 120 °C (entries 5 and 8). At higher temperature (150 °C) nonidentified side products were formed (entry 9). Among the various ligands tested, triphenylphosphine gave the highest

 
 Table 2. Carbonylation of 1 with Formamide in the Presence of Different Bases<sup>a</sup>

F <sub>3</sub> C	$H^{\text{Br}}$ + $H^{\text{O}}$ NH <sub>2</sub> -	Pd(OAc) <sub>2</sub> / 4 PPh <sub>3</sub> base 5 bar CO / 120 °C	F <sub>3</sub> C 4
entry	$base^b$	conv of <b>1</b> (%)	yield of <b>4</b> (%) <sup><math>d</math></sup>
1	DMAP	100	100
2	PPY <sup>c</sup>	99	97
3	$\mathbf{PPY}^d$	99	62
4	imidazole	100	96
5	1-methylimidazol	e 100	87
6	1,3,5-triazine	95	83
7	quinoline	100	78
8	pyrazole	100	78
9	2,4-lutidine	100	75
10	pyridine	100	69
11	2-picoline	100	64
12	pyrrole	54	54
13	pyrimidine	62	26

<sup>*a*</sup> Reaction conditions: **1** (35.6 mmol), base (38 mmol),  $Pd(OAc)_2$  (0.36 mmol), and ligand (Pd/P = 1:4) in 25 mL of formamide, in a 250 mL glass autoclave at 120 °C and 5 bar CO (initial pressure at room temperature) for 18 h. <sup>*b*</sup> GC yields. <sup>*c*</sup> PPY: 4-pyrrolidinopyridine. <sup>*d*</sup> With 10 mol % PPY and 1.1 equiv of NEt<sub>3</sub>.

yields (entry 5). With binap, dppb, dpephos, or dppf (entries 1–4), the yields were significantly lower. In situ formed palladium–phosphine complexes as commonly used for carbonylation reactions were well suited as catalysts, and similar results were obtained with different precursors such as PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, or PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> if the Pd/P ratio was the same (GC yield 95%). The CO pressure only influenced marginally the yields between 1 and 50 bar (entries 5, 10, 11, and 12). However, without CO the amide **4** was not formed (<2%), and the main product was the dehalogenated arene.

Among the different bases tested, the highest yields and the fastest reactions as judged from the pressure curves were obtained with DMAP and PPY (4-pyrrolidinopyridine) (Table 2). DMAP, PPY, and imidazole are known to be powerful Lewis bases and acylating catalysts,<sup>7</sup> indicating that the base has probably an additional role besides scavenging the formed acid. In the presence of 1 equiv of an ordinary base such as triethylamine, the amount of PPY could be reduced to 10 mol %, although the yields dropped from 97% to 62% (entries 2 and 3).

While good conversions were obtained in formamide as the solvent, the quantitative isolation of the products from the reaction mixture was difficult, and the isolated yields were generally lower than the GC yields. Advantageously, a variety of solvents, both polar and nonpolar, gave high yields using 2, 5, or 10 equiv of formamide, respectively. With only 1.1 equiv of formamide the yields were significantly lower (about 40% lower). Among the different solvents, *N*-methylpyrrolidinone (86% GC-yield) and dioxane (100% GC-yield) gave the best results.

The scope of the methodology was demonstrated using 1 mol %  $PdCl_2(PPh_3)_2$ , DMAP as base, 2 equiv of formamide and dioxane as the solvent. A variety of aryl and vinyl bromides were converted to the desired primary amides in good yields (Table 3). Aryl bromides with electron-withdrawing substituents (entries 1–3), 2-bro-

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 Table 3. Carbonylation of Aryl Halides to Primary Amides<sup>a</sup>



<sup>*a*</sup> Reaction conditions: aryl halide (35.6 mmol), DMAP (38 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.36 mmol), formamide (70 mmol) in 25 mL of dioxane, in a 250 mL glass autoclave at 120 °C and 5 bar CO (initial pressure at room temperature) for 18 h. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> DMAc as the solvent and with PPY. <sup>*d*</sup> DMF as the solvent and with imidazole. <sup>*e*</sup> DMAc as the solvent and with imidazole.

mopyridine (entry 4) and  $\beta$ -bromostyrene (entry 9) (all activated substrates) reacted rapidly, and generally the isolated yields were above 70%. The very low yields of the highly reactive 4-bromoacetophenone might be a consequence of side reactions with the acetyl group (entry 3). Less reactive substrates such as 2-chloropyridine (entry 5) and aryl bromides bearing electron-donating substituents (entries 7, 8, and 10) needed higher Pd/P ratios (up to 1:8) in order to stabilize the catalyst against decomposition to inactive palladium black.

Urea was also applied as an ammonia equivalent (entry 11), but the yield was significantly lower than with



**Figure 1.** Schematic pressure curve of the reaction of **1** with formamide in dioxane with DMAP as base in the presence of 1 mol % catalyst.



formamide. Because of the low solubility of urea in dioxane, DMAc (*N*,*N*-dimethylacetamide) had to be used as the solvent. Dimethylamides and methyl amides can also be prepared using DMF and *N*-methylformamide, respectively (entries 12 and 13). DMAc was tested as an alternative source of dimethylamine (entry 14) but gave lower yields than DMF.

During our investigations, we noticed an unusual run of the pressure curve (Figure 1). After the reaction temperature was reached, the pressure decreased rapidly in the first few hours until about 50% of the theoretical amount of CO was consumed. Then, the pressure increased again, until it became almost constant after 20 h.

If the reaction was stopped when the pressure minimum was reached, the aryl bromide was already consumed completely, but only 49% of the primary amide was formed. In addition, formylimide **5** (8%), dibenzoylimide **6** (2%) and the side products **7**, **8**, and **9** were identified (Scheme 1). Obviously **5** resulted from the reaction of formamide with an acyl-palladium complex, while **7**, **8**, and **9** were formed in subsequent reactions of imide **5** with formamide and amide **4**, respectively. We assume that these intermediates react to the primary



amide **4** in the further course of the reaction, since they were not found at the end of the reaction.

# Discussion

The simple procedure described here allows the preparation of a broad variety of primary amides, methylamides, and dimethylamides in one step starting from the corresponding aryl halides. The reaction conditions are reasonably mild to tolerate a variety of functional groups, although nucleophilic groups such as amines, alcohols, or thiols will probably interfere with the reaction. The protocol is very general for aryl bromides, and the only parameter to be adjusted is the Pd/P ratio. The main advantage of the method is the use of inexpensive and convenient to handle formamides as source of the amine moiety.

The reaction displayed some interesting features that raised the question about the mechanism and the role of the base. On the basis of our observations, we suggest that the aminocarbonylation proceeds as shown in Scheme 2. The first steps are in analogy to the accepted mechanism of the palladium-catalyzed carbonylation of aryl halides,<sup>8,9</sup> i.e., the aryl halide adds oxidatively to a palladium(0) complex,<sup>10</sup> followed by CO insertion to give an aroyl palladium species **10**. The presence of CO is a prerequisite for the formation of the aroyl species, explaining why the reaction does not proceed without a CO atmosphere (see above).

In the classical carbonylation reactions of aryl halides with amines or alcohols, the nucleophile reacts directly with the aroyl moiety **10**.<sup>9</sup> However, formamide is a very weak nucleophile, and an acylating catalyst such as DMAP, PPY, or imidazole is necessary for the transfer of the aroyl moiety to the formamide. GC analysis of the reaction mixture indicated that the imidazolide **11** was indeed formed (comparison with **11** synthesized by the reaction of 3-trifluoromethylbenzoyl chloride with imidazole), but too labile to be isolated. The proposed mechanism is supported by recent findings of Yoneyama et al.,<sup>11</sup> who described the formation of dibenzoylimide in the carbonylation of bromobenzene in the presence of benzamide. In addition, several examples of the intramolecular formation of cyclic imides are known in the literature.  $^{12} \ensuremath{$ 

The imide **5** decomposes slowly under the reaction conditions, but also undergoes side reactions with the excess of formamide as indicated by the formation of **7–9**. The formation and decomposition of the imide **5** nicely explains the observed run of the pressure curve (see Figure 1). In the first part of the reaction, the consumed CO is stored in the imide **5**, which upon decomposition to amide **4** releases CO in the further course of the reaction.

## Conclusions

Formamide is a convenient ammonia source for the preparation of primary amides by carbonylation of aryl halides. The new procedure is simple and efficient and avoids the use of expensive or difficult to handle reagents such as HMDS or ammonia, and the reactions can be carried out under mild conditions. For these reasons, the methodology is not only suitable for laboratory preparation, but has also the potential for large scale processes. The new protocol also allows the efficient synthesis of methylamides and dimethylamides with the corresponding formamides as amine sources.

### **Experimental Section**

**General Considerations.** For the carbonylation experiments, a 250 mL glass autoclave equipped with a magnetdriven hollow shaft stirrer was used. The reactions were carried out under nonisobaric conditions, and the progress of reaction was followed by measuring the pressure in the autoclave. CO gas (purity 99.97%) was purchased from Carbagas Chemical Co.

Commercially obtained materials were used as received without further purification. Aryl halides, ligands, reagents and solvents were purchased from Fluka Chemical Co. with the exception of 4-bromobenzotrifluoride (Aldrich Chemicals Co.) and 3-bromobenzotrifluoride (Novartis AG). Anhydrous dioxane (stored over molecular sieves) was used. Pd(OAc)<sub>2</sub> was purchased from Fluka Chemical Co., PdCl<sub>2</sub> (20% Pd in hydrochloric acid) from Degussa AG, and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> from Avocado Chemical Co. Dpephos was prepared according to a literature procedure.<sup>13</sup>

<sup>1</sup>H and <sup> $\hat{1}3$ </sup>C{<sup>1</sup>H} NMR spectra were recorded on a Bruker dpx 300 spectrometer. Chemical shifts ( $\delta$ ) are given in ppm and refer to TMS as internal standard. IR spectra were

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recorded on a Perkin-Elmer 1710 spectrometer. Melting points were measured with a Büchi 520 apparatus and are uncorrected. Gas chromatography was performed on a Fisons GC 8000 with a DB-17 column and helium as the carrier gas using di(ethylene glycol) di-*n*-butyl ether as internal standard. The combustion analyses were carried out by Solvias AG, Switzerland.

Typical Procedure for the Preparative Carbonylation Experiments

3-Trifluoromethylbenzamide (4) (Table 3, Entry 1). The autoclave was charged with 3-bromobenzotrifluoride (1) (8.01 g, 35.6 mmol), 4-(dimethylamino)pyridine (4.74 g, 38.0 mmol), formamide (3.12 g, 69.1 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (243 mg, 0.35 mmol, 1 mol %), and 1,4-dioxane (25 mL). The autoclave was purged three times with nitrogen (6 bar) and charged with 5 bar CO. The reaction mixture was heated to 120 °C. After 20 h and cooling to room temperature, the solvent was evaporated in vacuo. The residue was partitioned between dichloromethane and water. The aqueous layer was extracted twice with additional dichloromethane. The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane as eluent). An amount of 4.8 g (25 mmol, 71%) of 4 was obtained as colorless crystals.  $R_f = 0.24$  (EtOAc:hexane 1:1); mp: 121.5-122.0 °C (lit.:<sup>14</sup> 122–123 °C); <sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>, 297 K) δ 8.25 (s (br), 1H), 8.22-8.17 (m, 2H), 7.89 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.64 (s (br), 1H);  ${}^{13}C{}^{1}H$ NMR (75.5 MHz, DMSO- $d_{\!6}\!,$  297 K)  $\delta$  167.2, 136.0, 132.3, 130.3, 130.0 (q, J(C-F) = 32 Hz), 128.6 (q, J(C-F) = 4 Hz), 124.9 (q, J(C-F) = 4 Hz), 124.8 (q, J(C-F) = 272 Hz); IR (KBr, cm<sup>-1</sup>) 3333, 3152, 1667, 1628, 1588, 1400. Anal. Calcd for C<sub>8</sub>H<sub>6</sub>F<sub>3</sub>-NO: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.83; H, 3.21; N, 7.19.

For experiments under different conditions of temperature or CO pressure, or with other ligands and bases, the conditions given in the respective tables were used.

**Isolation of the Reaction Intermediates 5–9 (Scheme 1).** The experiment was carried out as described above. After 2 h at 120 °C, the reaction was stopped and the mixture was cooled to room temperature. The reaction mixture was worked up as described, and the products were purified by column chromatography (silica gel, EtOAc/hexane 1:2 as eluent).

**3-Trifluoromethylbenzamide (4)** was obtained as colorless crystals (3.3 g, 17.5 mmol, 49%).

*N***-Formyl-3-trifluoromethylbenzoylimide (5)** was obtained as colorless crystals (650 mg, 3.0 mmol, 8%).  $R_f = 0.54$  (EtOAc:hexane 1:2); mp: 130–130.5 °C; <sup>1</sup>H NMR (300.1 MHz, DMSO- $d_6$ , 297 K)  $\delta$  11.96 (d, J = 8.6 Hz, 1H), 9.28 (d, J = 8.4

(14) Lancaster Catalogue, 93/94.

Hz, 1H), 8.34 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.03 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H);  $^{13}C{}^{1}H$  NMR (75.5 MHz, DMSO- $d_6$ , 297 K)  $\delta$  167.2, 165.2, 133.6, 133.3, 130.8, 130.6 (q, J(C-F) = 4 Hz), 130.3 (q, J(C-F) = 32 Hz), 125.9 (q, J(C-F) = 4 Hz), 124.6 (q, J(C-F) = 272 Hz); IR (KBr, cm<sup>-1</sup>) 3246, 1740, 1678, 1469. Anal. Calcd for C<sub>9</sub>H<sub>6</sub>F<sub>3</sub>NO<sub>2</sub>: C, 49.78; H, 2.79; N, 6.45; F, 26.25; O, 14.74. Found: C, 49.89; H, 2.83; N, 6.27; F, 26.08; O, 14.75.

**Bis-(3-trifluoromethylbenzoyl)imide (6)** was obtained as colorless crystals (210 mg, 0.6 mmol, 3%).  $R_f = 0.50$  (EtOAc: hexane 1:1); mp: 177–178 °C; <sup>1</sup>H NMR (300.1 MHz, DMSO- $d_6$ , 297 K)  $\delta$  11.72 (s, 1H), 8.27 (s, 2H), 8.21 (d, J = 7.9 Hz, 2H), 8.01 (d, J = 7.8 Hz, 2H), 7.78 (t, J = 7.8 Hz, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (75.5 MHz, DMSO- $d_6$ , 297 K)  $\delta$  167.4, 135.7, 133.6, 130.6, 129.5 (q, J(C-F) = 26 Hz), 129.8, 126.1 (q, J(C-F) = 4 Hz), 124.7 (q, J(C-F) = 272 Hz); IR (KBr, cm<sup>-1</sup>) 3267, 1719, 1528, 1336. Anal. Calcd for C<sub>16</sub>H<sub>9</sub>F<sub>6</sub>NO<sub>2</sub>: C, 53.20; H, 2.51; N, 3.88. Found: C, 53.13; H, 2.58; N, 3.87.

7 was obtained as colorless crystals (120 mg, 0.21 mmol, 2%).  $R_f = 0.48$  (EtOAc:hexane 1:2); <sup>1</sup>H NMR (300.1 MHz, DMSO- $d_6$ , 297 K)  $\delta$  9.46 (d, J = 6.1 Hz, 3H), 8.28 (s, 3H), 8.23 (d, J = 7.8 Hz, 3H), 7.96 (dd, J = 7.8 Hz, 0.6 Hz, 3H), 7.77 (t, J = 7.8 Hz, 3H), 7.38 (q, J = 6.1 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (75.5 MHz, DMSO- $d_6$ , 297 K)  $\delta$  165.2 (3C), 135.4 (3C), 132.7 (3C), 130.6 (3C), 129.9 (q, J(C-F) = 32 Hz, 3C), 129.1 (q, J(C-F) = 4 Hz, 3C), 125.8 (q, J(C-F) = 272 Hz, 3C), 125.1 (q, J(C-F) = 4 Hz, 3C), 64.4.

**8** and **9** were obtained as a mixture consisting of 80% of **8** (520 mg, 1.2 mmol, 8%) and 20% of **9** (130 mg, 0.5 mmol, 1%). **8**: <sup>1</sup>H NMR (300.1 MHz, DMSO- $d_6$ , 297 K)  $\delta$  9.50 (d, J = 6.2 Hz, 2H), 8.94 (dd, J = 7.0 Hz, 1.3 Hz, 1H), 8.26 (s, 2H), 8.20 (d, J = 7.8 Hz, 2H), 8.09 (dd, J = 1.3 Hz, 0.8 Hz, 1H), 7.95 (dd, J = 7.8 Hz, 0.7 Hz, 2H), 7.75 (t, J = 7.8 Hz, 2H), 7.38 (q, J = 6.2 Hz, 1H). Additional signals for **9**:  $\delta$  9.50 (d, J = 6.2 Hz, 1H), 8.43–8.41 (m, 2H), 6.97–6.90 (m, 1H).

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**Supporting Information Available:** Spectral data (<sup>1</sup>H and <sup>13</sup>C NMR, IR, MS), elemental analysis and melting points of all primary amides. This material is available free of charge via the Internet at http://pubs.acs.org.

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