



# Binary additive effect of benzoic acid in *ipso*-Friedel-Crafts-type dearomatization of phenols using a chiral silver phosphate

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## ABSTRACT

We previously developed a chemoselective asymmetric phenol dearomatization using a silver catalyst and benzoic acid as an additive to enhance the reaction efficiency. The mechanistic role of the additive, however, remained unclear. Herein we describe detailed studies to elucidate the additive effect, which revealed that benzoic acid plays two supporting roles in the silver-catalyzed reaction. First, it promotes protonation of a silver enolate intermediate to improve the chemical yield of a spirolactam. Second, it dissociates a homochiral dimer of silver phosphate to generate a monomeric species.

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## 1. Introduction

The use of an additive in specific catalytic reactions often enhances the chemical yield and selectivity, or changes the entire reaction pathway. As a strategy to optimize reaction conditions, additives can be added directly to the reaction vessel, providing an easy and operator-friendly method as compared with redesigning the molecular structure of the catalyst or substrate.<sup>1</sup>

As part of our ongoing studies aimed at exploring the novel reactivity of metal carbenoid species,<sup>2,3</sup> we developed a chemoselective dearomative *ipso*-Friedel-Crafts (DIFC) reaction<sup>4</sup> of phenol derivatives using a silver catalyst, while a Rh or Cu catalyst caused a C–H insertion and Büchner reaction (Scheme 1)<sup>5,6</sup> The asymmetric DIFC reaction was realized by using chiral silver phosphate and benzoic acid as an additive,<sup>7</sup> which efficiently improved the yield without decreasing the enantioselectivity. The mechanistic role of the additive, however, remained unclear. Herein, we report detailed studies on the function of the benzoic acid in the silver carbenoid-

mediated enantioselective dearomatization, revealing that the additive has critical binary effects to improve the reaction efficiency.

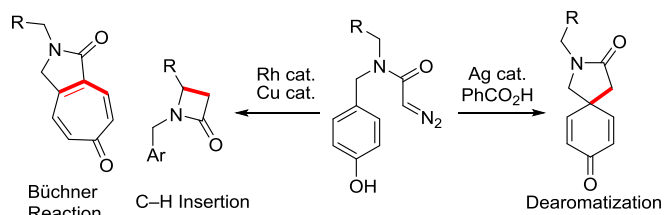
## 2. Results and discussion

Initially, we screened additives, including mainly carboxylic acid analogues (**A–F**), to evaluate the influence of structural modifications of the additive on an Ag-catalyzed DIFC reaction of phenol **1** possessing  $\alpha$ -diazoamide as a carbenoid precursor (Table 1). We first confirmed differences in the reaction yield between additive and additive-free conditions. The yield of spirolactam **2** under the reaction conditions using 1 equivalent of benzoic acid was 83% (entry 2), and the additive-free conditions produced **2** in 61% yield as well as side product **3** in 8% yield through a Büchner reaction followed by auto-oxidation (entry 1).<sup>8</sup> The reaction in the presence of benzoic acid derivatives **B** and **C** possessing an electron-withdrawing group or an electron-donating group gave **2** in 67%–80% yield with 87%–89% ee (entries 3 and 4). Sodium benzoate **D** interfered with the reaction progress, suggesting a complexation between (*S*)-TRIPAg and benzoate anion (entry 5). The use of (*R*)- or (*S*)-mandelic acid (**E**, **F**) furnished **2** with similar enantioselectivities, and no match or mismatch effect on stereochemistry was observed, indicating the non-involvement of carboxylic acid in the enantiodetermining step (entries 6 and 7). One equivalent of

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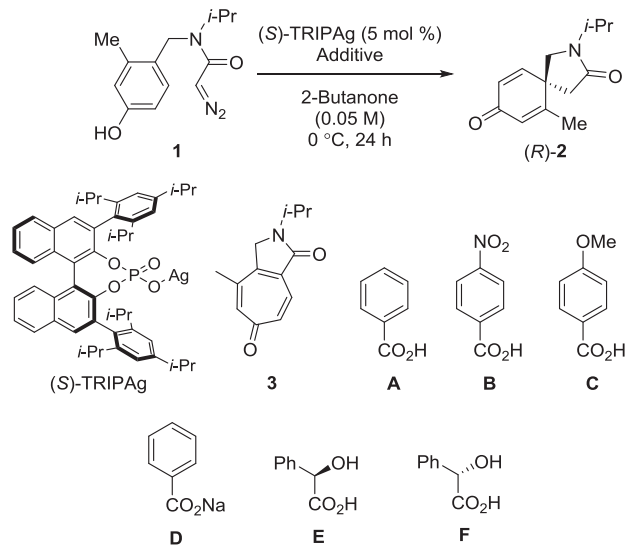
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**Scheme 1.** Intramolecular reactions of phenols with metal carbenoids.

**Table 1**  
Screening of additives.



**Scheme 2.** Two dissimilar reactions of enolate **4**.

**Scheme 3.** Base-promoted conversion from spirolactam to a Büchner-type product.

Entry	Additive (eq)	2 Yield (%)	ee (%)
1 <sup>a,b</sup>	None	61	90
2	<b>A</b> (1)	83	89
3	<b>B</b> (1)	67	87
4	<b>C</b> (1)	80	89
5	<b>D</b> (1)	2	n.d.
6	<b>E</b> (1)	86	86
7	<b>F</b> (1)	80	87
8	<b>A</b> (0.5)	77	86
9	<b>A</b> (2)	80	87

<sup>a</sup> Reaction was employed for 21 h.

<sup>b</sup> **3** was generated in 8% yield.

benzoic acid was suitable for the DIFC reaction (entries 1 vs 8, 9).

At an early stage of the reaction development, we used the additive based on a tentative working hypothesis that benzoic acid could promote protodemetalation of the enolate intermediate **4** generated from the reaction of a silver carbenoid with phenol and suppress the intramolecular 1,4-addition leading to Büchner-type product **7** (Scheme 2).

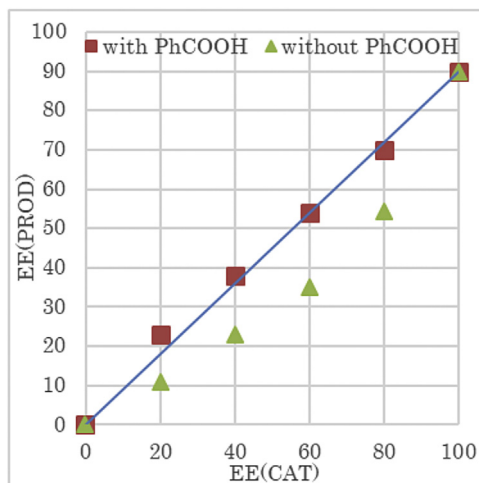
We examined the following reaction to check whether such a reaction course (**4** → **7**) occurs *via* highly strained cyclopropane **6** (Scheme 3).<sup>9</sup>

Treatment of the isolated spirolactam **8** with NaHMDS to generate the corresponding enolate, which could be regarded as a congeneric species of **4**, furnished **9** in 32% yield.<sup>10</sup> This might indicate that the side reaction giving **3** proceeded under additive-free conditions (Table 1, entry 1), and benzoic acid played a supplementary role for the prompt protonation of silver enolate **4** to competently enhance the chemical yield of the spirolactam.

Because silver phosphates<sup>11,12</sup> are known to form their dimeric

species or higher aggregates,<sup>13</sup> we next turned our attention to the possibility of an interaction between benzoic acid and the silver phosphate complex. Although the nonlinear effects are generally attributed to the formation of diastereomeric species or higher-order agglomerates,<sup>14,15</sup> asymmetric amplification was not observed in our previous studies when the enantiomeric excess of the silver catalyst was changed under the conditions using benzoic acid.<sup>5</sup> To investigate the influence of the additive, we next examined the asymmetric amplification under benzoic acid-free conditions, which exhibited negative nonlinear effects (Fig. 1). This observation led us to hypothesize an involvement of the aggregated catalyst species.

Taking the results of non-linear effect studies into consideration, the benzoic acid could influence the order dependency of the reaction with respect to the silver catalyst. While the reaction rate in the presence of 1 equivalent benzoic acid showed a first-order dependency on the catalyst based on the initial rate kinetics,<sup>5</sup> the reaction in the absence of the additive was half-order in the silver



**Fig. 1.** Studies of nonlinear effects.

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