



# Synthesis of phenylacetic acids under rhodium-catalyzed carbonylation conditions

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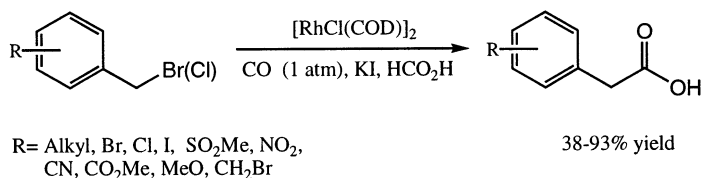
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## Abstract

Benzyl halides are efficiently carbonylated to phenylacetic acids in the presence of a catalytic amount of the dimer of chloro(1,5-cyclooctadiene)rhodium(I) in formic acid. Under these reaction conditions, sensitive functionalities such as esters and nitriles are tolerated and the phenylacetic acids are obtained in good to high yields. © 2000 Elsevier Science Ltd. All rights reserved.

Transition-metal catalyzed carbonylation of organic halides with carbon monoxide is one of the most useful methods for the direct introduction of a carbonyl group into organic molecules.<sup>1</sup> The use of catalysts such as  $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ ,<sup>2</sup>  $\text{CoCl}_2/\text{NaBH}_4$ ,<sup>3</sup>  $\text{Co}_2(\text{CO})_8$ ,<sup>4</sup>  $\text{Co}(\text{CO})_3\text{NO}$ ,<sup>5</sup>  $\text{Co}(\text{Ph}_3\text{P})_2\text{Cl}_2/\text{Bu}_4\text{NBr}$ <sup>6</sup> and  $\text{Fe}(\text{CO})_5$ <sup>7</sup> to convert benzyl bromides to esters or carboxylic acids has been studied. Most of these existing methods, however, employ either harsh reaction conditions or generate products in low yield. Recently, rhodium complexes have emerged as efficient transition-metal catalysts in carbonylation reactions.<sup>8</sup> The use of main group alkoxide in the presence of a rhodium catalyst has been the subject of several publications.<sup>9</sup> Also, the addition of a phase transfer catalyst in the presence of an inorganic base greatly increases the yields.<sup>10</sup> However, both methods provide the ester as the major reaction product while the corresponding acid is often present in low yield as a by-product. The direct formation of carboxylic acids under a rhodium catalyst is not well studied. Herein, we report the synthesis of phenylacetic acids under rhodium-catalyzed carbonylation conditions (Scheme 1).



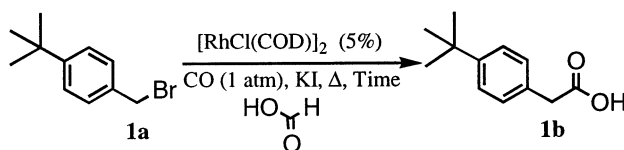
Scheme 1.

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Alper and co-workers have demonstrated that a *t*-butyl ester could be isolated in 49% yield by treatment of 4-methylbenzyl bromide in the presence 20 mol% of the dimer of chloro(1,5-hexadiene)rhodium(I) and a catalytic amount of potassium iodide (6 mol%) in *t*-butyl formate.<sup>11</sup> In our hands, however, the formation of the ester and the corresponding carboxylic acid as a side product in a 1.3:1 ratio was observed.<sup>12</sup> Therefore, we set out to determine if the direct formation of arylacetic acids could be achieved by rhodium catalysis using formic acid.

Our initial efforts were directed toward finding the optimal conditions using 4-(*t*-butyl)benzyl bromide (**1a**) as the substrate under different reaction conditions in formic acid (Table 1). The rhodium catalyst used for the study was the dimer of chloro(1,5-cyclooctadiene)rhodium(I) [RhCl(COD)]<sub>2</sub> (10 mol%). Increasing the temperature from 23°C (entry 1) to 60°C was beneficial as it decreased the reaction time to 18 h (entry 2). The absence of potassium iodide resulted in lower conversion (entry 3) and finally, in the presence of 5 mol% of KI at 60°C the benzyl bromide was completely converted to phenylacetic acid (**1b**) (entry 4).

Table 1  
Optimal reaction conditions



Entry	Conditions			Conversion (%) <sup>a</sup>
	KI (%)	Δ (°C)	Time (h)	
1	5	23	65	54
2	5	60	7	34
3	0	60	18	51
4	5	60	18	100

<sup>a</sup> Conversions were determined by <sup>1</sup>H NMR analysis and are based on the remaining 4-*t*-butylbenzyl bromide **1a**.

The carbonylation reaction of a variety of benzyl halides was then carried out using these optimized conditions and the results are summarized in Table 2.

The carboxylic acid of the model substrate (**1a**) was obtained in a high yield of 89% (entry 1). Similarly, carbonylation of the benzyl bromide **2a** cleanly provided phenylacetic acid **2b** in a 93% yield (entry 2). Under these reaction conditions the carbonylation occurs exclusively at the benzyl site, while aryl halides are not affected. For example, 4-bromobenzyl bromide (**3a**), 4-chlorobenzyl bromide (**4a**) and 3-iodobenzyl bromide (**9a**) were converted to the desired phenylacetic acid **3b**, **4b**, **9b** in yields ranging from 93 to 95% (entries 3, 4 and 9). On the other hand, the dibenzyl bromide (**8a**) gave an 89% yield of the dicarboxylic acid (**8b**) (entry 8). In this case, the temperature was raised to 90°C in order to achieve complete conversion. Similarly, the carbonylation of the benzyl bromide ester **6a** under these conditions provided the phenylacetic acid **6b** in 91% without any hydrolysis of the methyl ester (entry 6). In the case of the *p*-cyanobenzyl bromide (**7a**) the acid **7b** was obtained in a lower yield of 51% due to the conversion of the nitrile to the primary amide (entry 7). *Meta*- and *ortho*-substituted benzyl

Table 2  
Rhodium catalyzed carbonylation of benzyl halides in formic acid<sup>a</sup>

Entry	Substrate	$\Delta$ (°C)	Product <sup>b</sup>	Yield <sup>c</sup>
1	<i>p</i> - <i>t</i> -ButylC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>1a</b> )	60	<i>p</i> - <i>t</i> -ButylC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>1b</b> )	89
2	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>2a</b> )	60	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>2b</b> )	93
3	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>3a</b> )	60	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>3b</b> )	93
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>4a</b> )	60	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>4b</b> )	95
5	<i>p</i> -MeSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>5a</b> )	60	<i>p</i> -MeSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>5b</b> )	89
6	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>6a</b> )	75	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>6b</b> )	91
7	<i>p</i> -CNCC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>7a</b> )	60	<i>p</i> -CNCC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>7b</b> )	51
8	<i>p</i> -BrCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>8a</b> )	90	<i>p</i> -HO <sub>2</sub> CCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>8b</b> )	89
9	<i>m</i> -IC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>9a</b> )	60	<i>m</i> -IC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>9b</b> )	95
10	<i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>10a</b> )	60	<i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>10b</b> )	89
11	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>11a</b> )	80	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>11b</b> )	38
12	<i>o</i> -PhC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br ( <b>12a</b> )	90	<i>o</i> -PhC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>12b</b> )	78
13	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Cl ( <b>13a</b> )	85	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CO <sub>2</sub> H ( <b>2b</b> )	80
14	<i>o</i> -C <sub>5</sub> H <sub>4</sub> NCH <sub>2</sub> Cl ( <b>14a</b> )	90	<i>o</i> -C <sub>5</sub> H <sub>4</sub> NCH <sub>2</sub> CO <sub>2</sub> H ( <b>14b</b> )	0

<sup>a</sup> Reactions were carried out in formic acid at the indicated temperature using 10 mol% of catalyst in the presence of KI (5 mol%) under 1 atmosphere of carbon monoxide for 18 h.

<sup>b</sup> All new compounds were fully characterized and all analytical and spectral (IR, NMR, MS) data are fully consistent with the assigned structures. All known compounds were characterized by NMR.

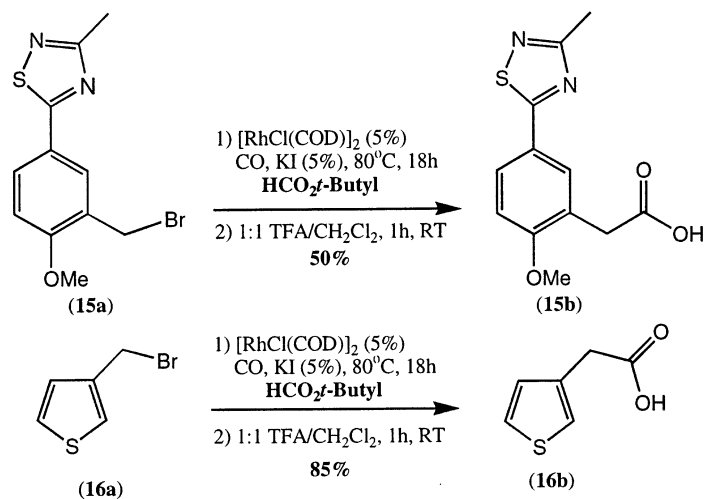
<sup>c</sup> Isolated yield.

bromides were also evaluated under these reaction conditions. The carbonylation of *m*-methoxybenzyl bromide (**10a**) and *m*-nitrobenzyl bromide (**11a**) were also successful, affording the arylacetic acids **10b** and **11b** in 95 and 38% yields, respectively (entries 10 and 11). In the case of *m*-nitrobenzyl bromide (**11a**), the reaction was carried out at 80°C since low conversion was observed at 60°C. Due to steric hindrance, the carbonylation of *o*-phenylbenzyl bromide (**12a**) was carried out at 90°C affording the acid **12b** in 78% yield. This method was shown not to be limited to benzylic bromides since the carbonylation of benzyl chloride (**13a**) provided phenylacetic acid (**2b**) in 80% yield.<sup>13</sup> Conversely, the carbonylation of 2-picoly chloride (**14a**) was unsuccessful.<sup>14</sup>

The carbonylation of the disubstituted benzyl bromide **15a** and 3-bromomethyl thiophene (**16a**) were also investigated. Under the aforementioned optimal reaction conditions only decomposition was observed. However, if the reactions were carried out in *tert*-butyl formate followed by hydrolysis of the crude mixture with 1:1 TFA/CH<sub>2</sub>Cl<sub>2</sub>, the acids were obtained in 50% yield for the phenylacetic acid **15b** and 85% yield for 3-thiophenylacetic acid (**16b**) (Scheme 2).

A typical procedure for the carbonylation is as follows: a flask charged with 4-(*tert*-butyl)benzyl bromide (**1a**) (300 mg, 1.3 mmol), KI (11 mg, 0.066 mmol) and [RhCl(COD)]<sub>2</sub> (33 mg, 0.066 mmol) in formic acid was flushed with nitrogen and then placed under 1 atmosphere of carbon monoxide and stirred at 60°C for 18 h. After cooling the solution to room temperature, the reaction mixture was then concentrated, diluted with ethyl acetate, washed with 1N HCl and brine and dried over MgSO<sub>4</sub>. Finally, purification on silica gel gave 226 mg (89%) of 4-(*tert*-butyl)phenylacetic acid (**1b**).

In summary, we have shown that the direct carbonylation of benzyl halides using the rhodium catalyst [RhCl(COD)]<sub>2</sub> leads to good yields of the corresponding acids. For sensitive substrates where direct carbonylation is problematic, a two-step method was shown to restore the high yields of the carbonylation process.



Scheme 2.

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