

## PALLADIUM(0)-CATALYZED CARBONYLATION ON THE MULTIPIN™ SYSTEM

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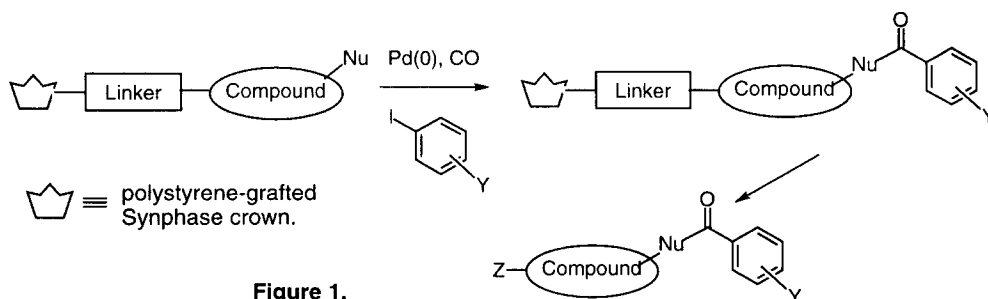
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**Abstract:** Pd(0)-catalyzed carbonylation using carbon monoxide and various aryl iodides with polymer-supported primary and secondary alcohols, and primary amines was accomplished.

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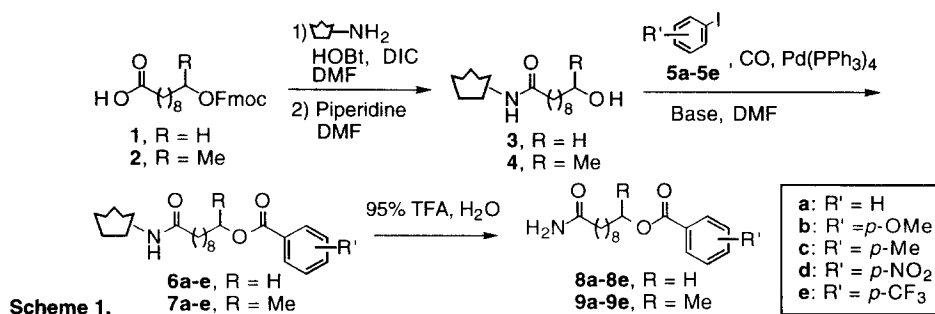
**Key words:** Amides, aryl halides, carbonylation, esters, palladium catalysts, solid-phase synthesis

The palladium(0)-catalyzed carbonylation of aromatic halides is one of the most versatile and convenient processes for the solution-phase preparation of aromatic carbonyl compounds, including key intermediates in natural product synthesis.<sup>1-3</sup> The combination of various aromatic halides and nucleophiles, such as alcohols and amines offers an attractive approach to a variety of corresponding carbonyl compounds. If these processes can be carried out on solid support, combinatorial sets of carbonyl compounds could be readily prepared. However, few solid phase reactions, such as hydrogenation<sup>4</sup> and hydroformylation<sup>5</sup> have been reported using gaseous reagents. We report here the preparation of esters and amides, including amino acid derivatives, via palladium(0)-catalyzed carbonylation of functionalized phenyl iodides and solid-supported alcohols and amines as shown in Figure 1. This work was performed on the Multipin system. The Multipin system has been used in the synthesis of chemical libraries.<sup>6</sup> We have also reported that rhodium(I)-catalyzed hydroformylation of 1,1-disubstituted alkene on polystyrene-grafted Synphase™ crowns successively provided the corresponding



aldehyde with good purity.<sup>5</sup>

Fmoc-protected 10-hydroxydecanoic acid (**1**) and 10-hydroxyundecanoic acid (**2**) were coupled onto Rink amine derivatized polystyrene crowns (DIC, HOBT, DMF, 20 °C, Scheme 1).<sup>7,8</sup> Complete conversion was demonstrated by a color test (negative result) with a solution of trinitrobenzenesulfonic acid in DMF / DIEA (10 : 1, v/v). After cleavage of the Fmoc group (20% piperidine / DMF), the crowns **3** and **4** were subjected to palladium(0)-catalyzed carbonylation conditions using several aryl iodides **5a-5e**, respectively. The obtained crowns **6** and **7** were washed, dried, and treated with 95% TFA-water to give the desired esters **8** and **9**, respectively. The crude products were analyzed by HPLC to compare the amount of product **8** or **9** with cleaved starting material. The purities of the products were also determined by HPLC and the structure of the respective major product was determined by NMR after collection by HPLC. The results are shown in Table 1.



**Table 1** Palladium-Catalyzed Carbonylation of **5a-5e** with **3** and **4**

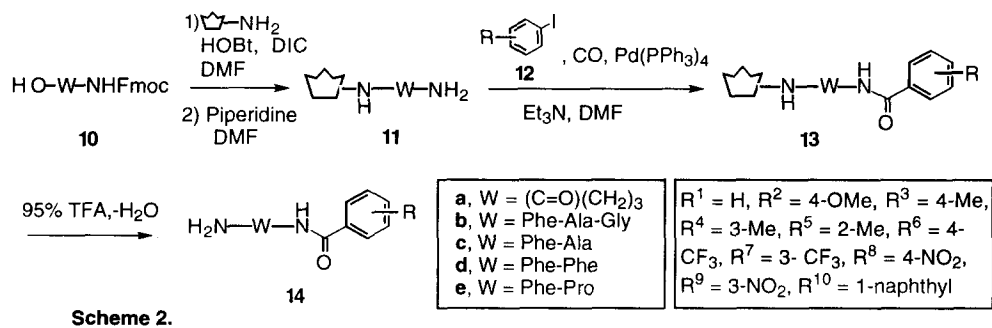
Entry <sup>a</sup>	Product	Time / h	Conv. / %	Purity <sup>c</sup> / %	Entry <sup>a</sup>	Product	Time / h	Conv. / %	Purity <sup>c</sup> / %
1	<b>8a</b>	96	93	80	6	<b>9a<sup>b</sup></b>	96	92	77
2	<b>8b</b>	96	86	84	7	<b>9b<sup>b</sup></b>	96	90	81
3	<b>8c</b>	96	91	91	8	<b>9c<sup>b</sup></b>	96	84	76
4	<b>8d</b>	48	>95	91	9	<b>9d</b>	48	>95	81
5	<b>8e</b>	48	>95	94	10	<b>9e<sup>b</sup></b>	96	95	85

<sup>a</sup> Conditions: Ar-I 0.5 M, NEt<sub>3</sub> 0.5 M, Pd(PPh<sub>3</sub>)<sub>4</sub> 0.01 M, CO 15 atm, DMF 80 °C;

<sup>b</sup> DMAP 0.1 M was added. <sup>c</sup> Determined by HPLC with peak area (refractive index).

The reaction proceeded in the presence of 0.01 M of tetrakis(triphenylphosphine)palladium under 15 atm of carbon monoxide with 0.5 M of aryl iodides and 0.5 M of triethylamine in DMF.<sup>9</sup> For the primary alcohol loading on the crowns with phenyl iodides including electron donating substituents needed 96 h completion of reactions (**8a**, **8b**, and **8c**) whereas for those having electron withdrawing substituents, the reaction completed within 48 h (**8d** and **8e**). The addition of 4-(dimethylamino)pyridine (0.1 M) was essential to complete the transformation of support-bound secondary alcohol **4** into **9**, with the exception of **9d**. All products were obtained in good purity (76-94%).

The Pd(0)-catalyzed carbonylation with solid-supported amines was utilized for the preparation of a peptide library using the combination of five solid-supported amines **11a-e** and ten aryl iodides **12** (R<sup>1</sup>-R<sup>10</sup>).<sup>9</sup> Solid-supported primary amine **11a**, tripeptide **11b**, and dipeptides **11c-e** including proline as a secondary amine underwent carbonylation in the presence of the palladium catalyst leading to various functionalized aryl amides **14** with high purities as shown in Table 2.



**Table 2** Variety of Products **14** by Palladium-Catalyzed Amidation of **12** with **11**

Entry <sup>a</sup>	<b>11</b>	<b>12</b>	Conv. <sup>b</sup> / %	Purity <sup>b</sup> / %	MS <sup>d</sup>	Entry <sup>a</sup>	<b>11</b>	<b>12</b>	Conv. <sup>b</sup> / %	Purity <sup>b</sup> / %	MS <sup>d</sup>
1	<b>a</b>	R <sup>1</sup>	>99	86 <sup>c</sup>	229.1	26	<b>c</b>	R <sup>6</sup>	>99	77	430.2
2		R <sup>2</sup>	97	89 <sup>c</sup>	259.1	27		R <sup>7</sup>	>99	80	430.2
3		R <sup>3</sup>	98	91 <sup>c</sup>	243.1	28		R <sup>8</sup>	>99	72	407.2
4		R <sup>4</sup>	99	91 <sup>c</sup>	243.1	29		R <sup>9</sup>	>99	85	407.2
5		R <sup>5</sup>	98	92 <sup>c</sup>	243.1	30		R <sup>10</sup>	>99	86	412.2
6		R <sup>6</sup>	>99	85	297.1	31	<b>d</b>	R <sup>1</sup>	92	90	438.2
7		R <sup>7</sup>	>99	84	297.1	32		R <sup>2</sup>	90	88	468.2
8		R <sup>8</sup>	>99	88	274.1	33		R <sup>3</sup>	92	88	452.2
9		R <sup>9</sup>	>99	89	274.1	34		R <sup>4</sup>	93	89	452.2
10		R <sup>10</sup>	>99	85 <sup>c</sup>	279.1	35		R <sup>5</sup>	94	84	452.2
11	<b>b</b>	R <sup>1</sup>	97	82	419.2	36		R <sup>6</sup>	96	73	506.2
12		R <sup>2</sup>	91	76	449.2	37		R <sup>7</sup>	99	72	506.2
13		R <sup>3</sup>	91	75	433.2	38		R <sup>8</sup>	>99	77	483.2
14		R <sup>4</sup>	97	83	433.2	39		R <sup>9</sup>	>99	85	483.2
15		R <sup>5</sup>	95	86	433.2	40		R <sup>10</sup>	>99	80	488.2
16		R <sup>6</sup>	>99	84	487.2	41	<b>e</b>	R <sup>1</sup>	83	86 <sup>c</sup>	388.2
17		R <sup>7</sup>	>99	75	487.2	42		R <sup>2</sup>	76	89 <sup>c</sup>	418.2
18		R <sup>8</sup>	>99	84	464.2	43		R <sup>3</sup>	83	74 <sup>c</sup>	402.2
19		R <sup>9</sup>	>99	90	464.2	44		R <sup>4</sup>	83	78 <sup>c</sup>	402.2
20		R <sup>10</sup>	>99	93	469.2	45		R <sup>5</sup>	84	75 <sup>c</sup>	402.2
21	<b>c</b>	R <sup>1</sup>	>99	73	362.2	46		R <sup>6</sup>	>99	82	456.2
22		R <sup>2</sup>	81	83	392.2	47		R <sup>7</sup>	94	86	456.2
23		R <sup>3</sup>	85	65	376.2	48		R <sup>8</sup>	>99	88	433.2
24		R <sup>4</sup>	88	79	376.2	49		R <sup>9</sup>	>99	84	433.2
25		R <sup>5</sup>	89	79	376.2	50		R <sup>10</sup>	>99	79	438.2

<sup>a</sup> Conditions: Ar-I 0.5 M, NEt<sub>3</sub> 0.5 M, Pd(PPh<sub>3</sub>)<sub>4</sub> 0.01 M, CO 15 atm, DMF 80 °C, 12 h; <sup>b</sup> Conversion and purity were determined by HPLC (ODS column, 90 / 10 MeCN / H<sub>2</sub>O containing 0.1% TFA) with peak area (UV) at 214 nm; <sup>c</sup> Double carbonylation (ref 10,11) detected by Mass spectra (10-30%) was included; <sup>d</sup> Electrospray-TOF Mass data were recorded as [M+NH<sub>4</sub>]<sup>+</sup> on a PE Biosystems Mariner.

In summary, we have demonstrated the application of palladium(0)-catalyzed carbonylation to the preparation of diverse amides and esters from support-bound primary and secondary alcohols and amines, respectively. Use of the method was illustrated in the preparation of a peptide analogue library.

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7. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787-3790; Rink amine crowns were prepared from Fmoc-NH-Rink-Polystyrene crowns by treatment with 20% piperidine in DMF for 20 min before use. Batch no. 810-1, Loading = 9.5  $\mu\text{mol}$  per crown, Chiron Technologies Pty. Ltd.
8. DIC = diisopropylcarbodiimide, HOBt = 1-hydroxybenzotriazole
9. *Experimental*: Rink amine crowns were treated with Fmoc-protected amino (or hydroxy) carboxylic acid (0.1 M), DIC (0.1 M), and HOBt (0.1 M) in DMF at room temperature. After being left for 12 h, the crowns were washed three times with DMF and three times with methylene chloride. The obtained Fmoc-protected crowns were treated with 20% piperidine in DMF to provide deprotected amine (or alcohol). The coupling steps were repeated if needed, and the crowns were placed into sample tubes, to which a solution of Pd(PPh<sub>3</sub>)<sub>4</sub> (11.5 mg), NEt<sub>3</sub> (100  $\mu\text{L}$ ), and aryl halides (0.5 M) in DMF (1.0 mL) were added, respectively. The tubes were placed in an autoclave, which was purged with carbon monoxide three times before applying a pressure of 15 atm. After being left at 80 °C for 12 h, the acylated crowns **7** (or **3**) were consecutively washed with DMF (3 times), dichloromethane (twice), DMF (twice), acetonitrile (twice), 50% acetonitrile in water (4 times), methanol (3 times), and dichloromethane (3 times) and dried *in vacuo*. The cleavage was performed by treatment with 95% trifluoroacetic acid (TFA) in water for 1 h. The crude products were subjected to HPLC and mass spectral analyses.
10. Double carbonylation was detected on iodobenzene systems with electron-donating substituents. This result is identical with that reported in an elegant work of double carbonylation; see, Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235-3245.
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