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Palladium-Catalyzed Direct Carboxylation of Aryl Bromides with Carbon Dioxide

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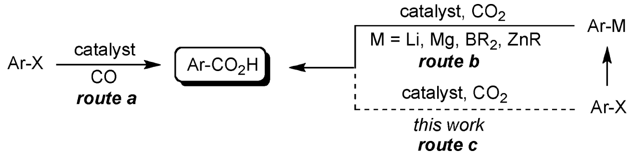
Because of its abundance, low cost, nontoxicity and high potential as a renewable source, carbon dioxide (CO_2) has recently gained considerable momentum as the ideal C1 source.[1] As a result, CO_2 fixation has become an active area of research in both academic and pharmaceutical laboratories.

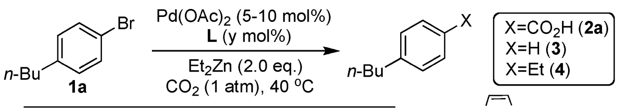
Benzoic acids are important motifs found in many natural and medicinally important compounds.[2] In recent years, metal-catalyzed carbonylation of aryl halides (Scheme 1, route a)[3] and carboxylation of carbon nucleophiles with CO_2 (Scheme 1, route b)[4,5] have become powerful alternatives to the classical synthetic approaches for these compounds. Despite the remarkable advances realized, the high toxicity associated with CO (route a) as well as the required synthesis of the employed organometallic reagents (route b) still represent important issues to be overcome. Ideally, the most straightforward route to benzoic acids from both a fundamental and practical point of view would imply the direct CO_2 insertion into aryl halides in a catalytic manner (Scheme 1, route c). To the best of our knowledge, no examples of this transformation have yet been reported in the field of homogeneous catalysis.[6] Herein, we present our initial studies on the direct Pd-catalyzed carboxylation of readily available aryl bromides with CO_2.

Scheme 1

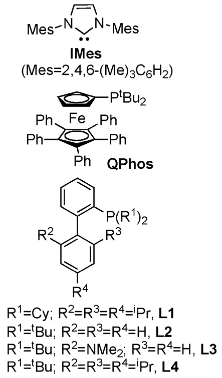


Prompted by stoichiometric experiments reported by Osakada and Yamamoto,[7] we initially focused our efforts on the conversion of nonactivated **1a** under atmospheric pressure of CO_2 using nickel catalysts. To render the process catalytic we used Et_2Zn as the reducing agent, a similar strategy that has been described by Iwasawa,[8a] Rovis,[8b] and Mori[4a,8c,d] for the efficient carboxylation of pronucleophiles with CO_2. After considerable experimentation, the targeted benzoic acid **2a** was obtained, albeit in low yields.[9] In striking contrast, Pd-based catalysts proved to be more promising for the transformation highlighted in Scheme 1 (route c). Therefore, the effect of variables such as palladium precatalyst, ligand, solvent, and temperature were systematically examined (Table 1).[9] In all cases studied, significant amounts of dehalogenated and Negishi-type products, **3** and **4**, respectively, were observed.[10] Among all the ligands examined,[9] we found that **L4**[11] showed the best activity by suppressing the formation of **4** (entry 8). This remarkably different reactivity to that observed with other simple phosphines (entries 1, 2, and 4), carbenes (entry 3), or analogous biarylphosphine ligands (entries 5, 6, and 7) could be tentatively attributed, at present, to the higher bulkiness of the resulting palladium intermediates. Notably, the nature of the solvent had also a crucial impact on the reaction outcome. Thus, while DMA and DMF clearly favored the carboxylation, NMP or DMSO resulted in the exclusive formation of **3** and **4**. Interestingly, the use of diethylacetamide, structurally related to DMA, led to the preferential formation of **4**, thus indicating the subtleties of this system (entry 12). Substitution of Et_2Zn by other reducing agents had also a deleterious effect, affording preferentially **3** and **4**.[9] The best results were finally obtained by operating at a higher CO_2 pressure (10 atm), thus leading to formation of **2a** in 64% isolated yield (entry 13).

Table 1. Screening of Reaction Conditions[a]



entry	**L** (y mol%)	Solvent	**2a**(%)[b]	**3**(%)[b]	**4**(%)[b]
1	PCy_3 (20)	DMA	0	0	99
2	P^tBu_3 (20)	DMA	0	0	99
3	IMes·HCl (20)	DMA	0	0	0
4	QPhos (20)	DMA	0	0	99
5	**L1** (20)	DMA	0	0	99
6	**L2** (20)	DMA	0	0	99
7	**L3** (20)	DMA	0	0	99
8[c]	**L4** (10)	DMA	56	24	0
9[c]	**L4** (10)	DMF	19	28	27
10[c]	**L4** (10)	NMP	0	99	0
11[c]	**L4** (10)	DMSO	0	31	69
12[c]	**L4** (10)	DEA	0	19	81
13[c,d]	**L4** (10)	DMA	64[e]	17	0



[a] **1a** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), solvent (0.25 M), CO_2 (1 atm), and Et_2Zn (1.0 mmol, 1 M in hexanes), 40 °C. [b] GC yields using dodecane as internal standard. [c] Using $Pd(OAc)_2$ (5 mol %). [d] CO_2 (10 atm). [e] Isolated yield. DEA = Diethylacetamide.

Encouraged by these initial results, we turned our attention to the scope of this reaction (Table 2). A wide range of substituted aryl bromides bearing both electron-donating and electron-withdrawing groups smoothly underwent the target carboxylation delivering the corresponding benzoic acids in moderate to good yields (Table 2).[12] The chemoselectivity of this novel transformation was clearly demonstrated by the tolerance of functional groups such as amines (entry 4), ethers (entry 5), thioethers (entry 6), alkenes (entry 10), esters (entry 11), and also heterocycles (entries 18 and 19). Additionally, ketones (entries 12 and 13) and even oxiranes (entry 14) remained inert under these reaction conditions, thus representing an additional bonus when comparing with the classical protocols involving the use of Grignard reagents or organolithiums. Moreover, the carboxylation reaction can be achieved in the presence of an aryl chloride, thus leaving options for subsequent manipulation (entry 8). Interestingly, the process was not hampered by *ortho* substituents (entries 16 and 17).

Given that organozinc derivatives are often prepared by reaction of Et_2Zn with aryl iodides,[13] we wondered whether organozinc

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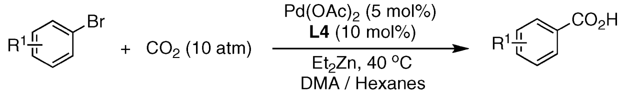
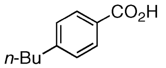
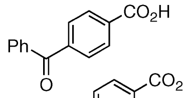
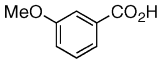
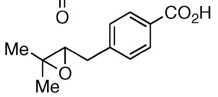
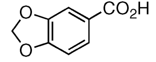
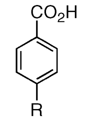
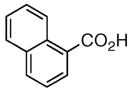
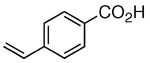
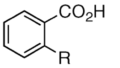
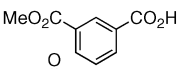
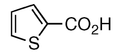
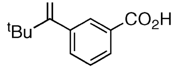
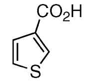
species were the actual reaction intermediates in our carboxylation protocol. To probe this hypothesis, PhZnBr was submitted to the catalytic reaction conditions, in both the presence and absence of Et$_2$Zn. Interestingly, no benzoic acid was formed and benzene was detected as the sole product in 91 and 96% GC yield, respectively. Furthermore, no deuterium incorporation in **3** was found when quenching the model reaction (entry 13, Table 1) with D_2O. Consequently, we believe these experiments rule out the intermediacy of organozinc species. Additional control experiments with **1a** also indicated that, in the absence of metal, ligand, or Et$_2$Zn, no reaction took place.[9] Although a detailed mechanistic picture requires further studies, our proposed catalytic cycle implies a challenging CO$_2$ insertion into the Pd−aryl bond[14] of an initially formed **A**[15] (Scheme 2) to yield **B**. Subsequently, transmetalation with Et$_2$Zn would deliver the zinc carboxylate **C**, with concomitant release of **D**, which ultimately would lead to the regeneration of the catalytic L$_n$Pd(0) species. At present, we cannot exclude the intermediacy of Pd(IV) species **E**, which would subsequently undergo reductive elimination to afford **B**. In full accordance with the mechanistic proposal, we can rationalize the formation of **3** and **4** by competitive transmetalation of Et$_2$Zn with intermediate **A** followed by either β-hydride elimination or reductive elimination, respectively.[16]

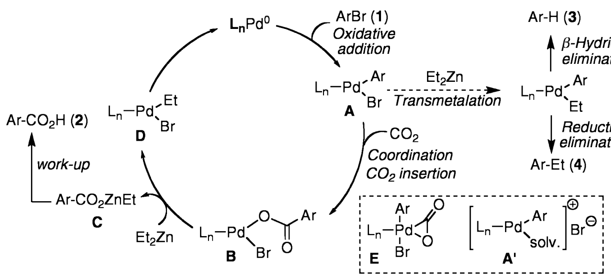
Table 2. Pd-Catalyzed Carboxylations of Aryl Bromides with CO$_2$[a]



entry	product	yield(%)[b]	entry	product	yield(%)[b]
1		64 82[c]	13		40
2		62	14		50
3		68			
4 5 6 7 8 9		R=NMe$_2$, 40 R=OTHP, 70 R=SMe, 68 R=CF$_3$, 43 R=Cl, 68 R=CHO, 63[d]	15		72
10		64	16 17		R=Me, 72 R=OMe, 63
11		57	18		67
12		67	19		61

[a] Reaction conditions: as in Table 1, entry 13. [b] Isolated yields, average of at least two runs. [c] 1.5 mmol scale. [d] Using 4-bromobenzaldehyde dimethyl acetal as starting material.

Scheme 2. Proposed Catalytic Cycle



In summary, we have developed a novel palladium catalyst system for the carboxylation of aryl bromides with CO$_2$. In contrast to other catalyst systems designed for similar purposes,[4,5] there is no need to prepare the corresponding organometallic intermediates, thus constituting an additional advantage in practical and economical terms. We believe this transformation constitutes a straightforward alternative for the synthesis of benzoic acids using CO$_2$ as the sole source of carbon. In further studies we aim to unravel the mechanism and fully explore the preparative scope of this reaction.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In contrast to ArBr, vinyl bromides did not give rise to the corresponding carboxylic acids; furthermore, ArI, ArCl, and ArOTf were found to be less efficient. See ref 9 for more details.

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(15) As the reaction is best performed in DMF or DMA, we can not rule out the intermediacy of palladium cationic complexes **A′** as well.

(16) Compound **3** does not come from decarboxylation of **2a**. See ref 9.

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