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Exceptionally simple catalytic system for the carbonylation of benzyl halides

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A ligand-less catalytic system, $Pd(OAc)_2$ immobilized in NBu_4Hal melt is suggested for the synthesis of arylacetic acids by the carbonylation of benzyl bromides.

Arylacetic acids and their derivatives have received attention because they are versatile intermediates in the synthesis of a vast range of pharmaceuticals, cosmetics and fragrances.[1] The transition metal-catalyzed carbonylation of benzyl halides is common and direct route to arylacetic acids and their esters. This reaction was intensively studied in past in common solvents, as well as water-organic solvent biphasic media.[2] Nowadays low melting point organic salts (ionic liquids) are widely explored as non-volatile, non-flammable and tunable substitutes of common solvents in chemistry and catalysis.[3] In particular, some benzyl chloride derivatives have been carbonylated recently in $[bmim]PF_6$ medium in the presence of 1–2% $PdCl_2(PPh_3)_2$ and NaOH water solution.[4]

In our recent works, efficient and recyclable catalytic systems Pd/NBu_4X/acid (X = Cl, Br; acid = TsOH, HBr) have been proposed for the hydrocarboxylation of styrene,[5,6] aliphatic olefins[7] and alcohols.[6,8] Importantly, a phosphine-free palladium catalyst immobilized in Br^--containing molten salts was found to be more active in hydrocarboxylation than traditional Pd phosphine complexes.[6–9] We tested similar systems in hydroxycarbonylation of benzyl halides and discovered, quite surprisingly, that the reaction proceeds smoothly in the absence of phosphine ligand, as well as base.

Benzyl chloride can be converted into benzylacetic acid in molten salt media in the presence of $Pd(OAc)_2$ as a catalyst precursor with good or excellent yields (Table 1). An amount of toluene, the product of $PhCH_2Cl$ reduction, was formed in some runs. No phosphines or other special ligands are needed to perform the reaction. Moreover, $PdCl_2(PPh_3)_2$ seemed to be less active than $Pd(OAc)_2$ (run 7). Reaction proceeds smoothly in the absence of stoichiometric amount of base, unlike usual protocol for halides carbonylation.[2] What is more, slight acidifying reaction mixture leads to only a little decrease in the yield (run 2), while adding 1.5 equiv. of NBu_3 makes a strong negative impact on carbonylation (run 6). The efficiency of various molten salts and ionic liquids as a reaction medium is as follows: NBu_4Cl > > NBu_4Br > NBu_4I > [bmim]Cl > [bmim]Br >> $[bmim]PF_6$ ≈ ≈ $[bmim]BF_4$. The best results were obtained with NBu_4Cl as a reaction medium. Phenylacetic acid yield reached 97% at 5 MPa (run 8) and 81% at 0.5 MPa (run 9).

As far as tetrabutylammonium halides are rather expensive materials, we tried to diminish their amount in catalytic run as low as possible. Pretty good results were obtained at an NBu_4Cl/substrate molar ratio of 0.88–1.75: phenylacetic acid yield was 93–97%, no toluene was formed (runs 8, 10). However, further decrease in NBu_4Cl/substrate ratio lead to lower yield of the acid (runs 11, 12). Possible explanation of this finding is increased dilution of NBu_4Cl by water, amount of which was constant in all the runs. Apparently, diluted NBu_4Cl cannot

$$ArCH_2X + CO + H_2O \xrightarrow[-HX]{Pd(OAc)_2/NBu_4X'} ArCH_2COOH$$

X, X′ = Cl, Br

Ar	X	Yield (%)
Ph	Cl	91
Ph	Br	69
4-$Bu^tC_6H_4$	Br	84
2-ClC_6H_4	Cl	96
3-ClC_6H_4	Cl	85
4-ClC_6H_4	Cl	84
3,4-$Cl_2C_6H_3$	Cl	90
3,4-$(CN)_2C_6H_3$	Cl	85
α-$C_{10}H_7$	Cl	92

Scheme 1 *Reagents and conditions*: 4 mmol of substrate, 8 μmol of $Pd(OAc)_2$, 8 mmol of H_2O, 1 g of NBu_4Cl. P = 5 MPa, T = 110 °C, 4 h.

Table 1 Hydrocarbonylation of benzyl chloride in molten salt media. Conditions: 4 mmol of substrate, 8 μmol of $Pd(OAc)_2$, 8 mmol of H_2O, molten salt. T = 110 °C, 2 h.

Run	Medium/g	Pressure/ MPa	Yield, GLC (%)	
			$PhCH_2COOH$	PhMe
1	NBu_4Br, 2	5.0	95.4	3.0
2[a]	NBu_4Br, 2	5.0	93.2	2.0
3	NBu_4Br, 2	2.5	92.5	4.0
4	NBu_4Br, 2	1.0	86.4	7.5
5	NBu_4Br, 2	0.5	54.2	12.8
6[b]	NBu4Br, 2	0.5	12.4	0
7[c]	NBu_4Br, 2	0.5	49.2	6.5
8	NBu_4Cl, 2	5.0	96.6	0
9	NBu_4Cl, 2	0.5	80.7	0
10	NBu_4Cl, 1	5.0	93.3	0
11	NBu_4Cl, 0.5	5.0	86.4	0.3
12	NBu_4Cl, 0.25	5.0	51.0	0.3
13	NBu_4I, 2	0.5	8.2	2.0
14	[bmim]Cl, 2	5.0	66.2	0
15	[bmim]Br, 2	5.0	48.1	5.0
16	$[bmim]PF_6$, 2	5.0	0	0
17	$[bmim]BF_4$, 2	5.0	0.1	1.2

[a]0.1 equiv. TsOH was added. [b]1.5 equiv. NBu_3 was added. [c]$PdCl_2(PPh_3)_2$ as a precursor.

solvate palladium effectively enough. Thus, catalyst activity decreases when water/NBu_4Cl molar ratio is 4.4 or higher.

Carbon monoxide pressure is essential limiting factor of the reaction. It seems that poor solubility of CO in ionic melt[3(e)] slows CO addition to Pd catalytic complex down. However, pressure effect is lower for NBu_4Cl (entries 8, 9) than for NBu_4Br (entries 1, 3–5). Carbonylation of benzyl chloride and its reduction into toluene seems to be competing reactions. Upon pressure decrease, carbonylation was suppressed while toluene formation increased (entries 1, 3–5).

Conceivable route for toluene formation is water gas shift reaction followed by catalytic hydrogenation over Pd black formed in some runs:

$$CO + H_2O \longrightarrow CO_2 + H_2,$$

$$PhCH_2Cl + H_2 \longrightarrow PhMe + HCl.$$

Indeed, we observed positive correlation between Pd black precipitated in the reactor and toluene yield in each run. In run 3, GC analysis revealed 0.04 vol.% CO_2 in a gas phase when the reaction was complete. However, the calculated yield of H_2 in WGS reaction proved to be 3.5%, somewhat less than the yield of toluene in run 3.

Decreasing palladium concentration in the reaction mixture is known to improve specific activity of the catalyst (*i.e.*, amount of product formed per mole of metal charged) in the Heck reaction.[10] In order to reach maximal TOF value in our reaction, catalyst amount was decreased to 0.05 mol% based on substrate. In NBu_4Br medium, phenylacetic acid yield was of 34% in 2 h run, corresponding average TOF 340 h^{-1}. In NBu_4Cl medium, 47% yield was reached with average TOF 470 h^{-1}. For comparison, phenylacetic acid was obtained[4] with the yield of 47% in a 24 h experiment, giving TOF value of about 2.

The question about stabilization of zero-valent palladium in the reaction mixture is open. Somewhat speculatively, highly dispersed Pd particles can be formed in NBu_4Hal melt, similar to those found in the Heck reaction.[10] Another way is the formation of $[Pd_2(CO)_nHal_m]^{m-}$ complexes with bridging CO ligands.[11]

A number of benzyl halides were successively converted into correspondent arylacetic acids.† Note that considerable amount of toluene (23% yield) was formed in benzyl bromide carbonylation while 4-*tert*-butylbenzyl bromide reacted more selectively giving only 2% 4-*tert*-butyltoluene. Quite pure arylacetic acids were obtained *via* correspondent Na salts by treating diethyl ether solution of raw acid with aqueous NaOH, separating water layer, acidifying with HCl and extracting benzylic acid with diethyl ether.

As a result, simple base-free and phosphine-free catalytic systems for benzyl halides carbonylation have been elaborated. Application of tetrabutylammonium halide melts as reaction media allows one (*a*) to avoid formation of stoichiometric amounts of halide salt as a co-product and (*b*) to exclude expensive, toxic and readily degradable phosphines from the catalyst formula.

† Catalytic runs were carried out in a pressurized 50 ml Hastelloy lined steel reactor equipped with a magnetic stirrer, arrangements for automatic temperature control and pressure regulation. The reactor was charged with 4 mmol of substrate, appropriate amounts of $Pd(OAc)_2$, 8 mmol of water and molten salt, flushed with CO and filled with CO up to desired pressure. Then, the stirrer was switched on and the reactor was heated to 110 °C. Upon CO consumption, the pressure was maintained constant by automatic pressure regulator. After reaction complete the reactor was cooled to ambient temperature and depressurized, the reaction mixture was extracted with diethyl ether and analyzed by GC.

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