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Ruthenium-catalyzed methoxycarbonylation of styrene

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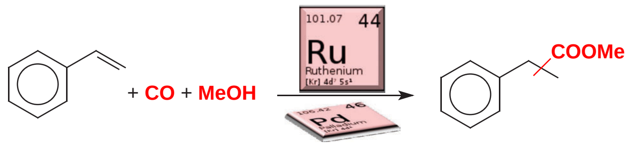
Methoxycarbonylation of styrene in the presence of homogeneous Ru catalysts is reported for the first time. Available $Ru_3(CO)_{12}$ together with halide source such as [bmim]Br, NaBr or LiCl represents active and easy to handle methoxycarbonylation catalyst. The key advantage of the new catalytic systems over traditional Pd catalysts is their high activity at CO pressure as low as 5 bar.



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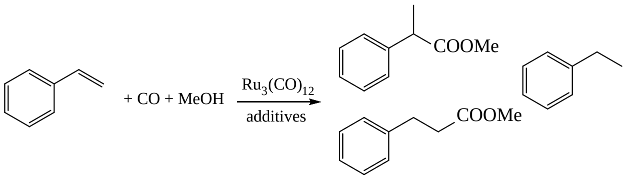
Catalytic carbonylation of unsaturated compounds is direct, one-stage, atom-efficient route to carboxylic acids and their derivatives such as esters, anhydrides, amides, lactones, lactams, *etc*.[1–5] Since classic work of Reppe,[6] a wide variety of transition metal complexes has been proposed as catalysts for hydroxyl- and methoxycarbonylation of alkenes and alkynes.[1] Although Ni and Co carbonyls were first used as industrial catalysts,[7] Pd–organophosphine complexes have attracted much attention owing to their high activity in mild conditions and tunable regioselectivity.[8] They have been successfully used for preparation of a range of important industrial products. For example, Lucite ‘Alpha’ technology for methyl methacrylate production has been commercialized in 2008. This process combines Pd-catalyzed methoxycarbonylation of ethylene into methyl propionate and its subsequent condensation with formaldehyde into MMA.[9]

Unfortunately, the drawbacks of palladium catalysts are the high cost of the metal and necessity of organophosphine ligands to maintain Pd in a homogeneous state. That is why searching for alternatives to palladium is an important task of the transition metal catalysis. Among noble metals, ruthenium is the least expensive and its complexes are widely applied in homogeneous catalysis.[10] In particular, Ru catalysts have been proposed for C1 chemistry such as hydroformylation[11–13] and alcoxycarbonylation of olefins with formic acid derivatives[14,15] and carbon dioxide.[16] However, ruthenium-catalyzed carbonylation of unsaturated compounds with carbon monoxide remains largely unexplored. The only report of Beller’s group describes alkoxycarbonylation of cyclohexene and some other alkenes in the presence of $Ru_3(CO)_{12}$.[17]

Vinyl arenes are important substrates for carbonylation because the resulting 2-arylpropanoic acids represent an important class of commercially applied non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen and ketoprofen.[18] Isomeric 3-arylpropionic acids also exhibit a wide range of biological activities including anti-bacterial, anti-convulsant, anti-cancer and analgesic activities.[19,20] Herein, we report our results on the Ru-catalyzed methoxycarbonylation of styrene as a model representative of vinylaromatic compounds.



Scheme 1 Methoxycarbonylation of styrene.

Linear and branched isomers of methyl phenylpropionate are target products formed in the styrene methoxycarbonylation. In some experiments, ethylbenzene and unidentified polymers were also detected in minor amounts (Scheme 1).

We used ruthenium carbonyl complex $Ru_3(CO)_{12}$ as a catalyst precursor.[21] Based on Beller‘s report,[17] halide anion was added as a key promoter, reaction temperature of 130 °C and CO pressure of 10 bar were chosen for initial screening. 1-Butyl-3-methylimidazolium (bmim), tetrabutylammonium (TBA) and tetramethylammonium (TMA) salts as well as some inorganic halides (Table 1) were tested as halide sources (see Online Supplementary Materials for the experimental details).

Styrene was found to be much more reactive in methoxycarbonylation then aliphatic alkenes. Indeed, 76% cyclohexene conversion and 70% methyl cyclohexanecarboxylate yield were reported[17] in the presence of 1 mol% $Ru_3(CO)_{12}$ and 200 mol% [bmim]Cl for 48 h, while in our experiment with the use of the same amount of the catalyst and the promoter 100% styrene conversion and 93% yield were achieved in 4 h (Table 1, entry 1). Decreasing $Ru_3(CO)_{12}$ loading to 0.33% resulted in the reducing the yield to 63% (entry 2). However, [bmim]Br and tetraalkylammonium halides appeared to be more active promoters and provided high yield of target esters (entries 3–7). Among inorganic halides, NaBr and LiCl showed the highest yield, apparently due to their better solubility in methanol in comparison with other salts (entry 12). In the presence of hydrochloric acid, though 22% conversion was achieved, no carbonylation products were detected. Likely, oligomerization of styrene occurred (Table 1, entry 13). Combination of [bmim]Br and TsOH as well as heavy metals halides promoters also gave

Table 1 Effect of halide on styrene methoxycarbonylation.^{a}

Entry	Halide (mol%)	Conversion (%)	Esters		Ethylbenzene yield (%)
			yield (%)	iso : n	
1^b	[bmim]Cl (200)	100	93	0.84	6
2	[bmim]Cl (200)	67	63	0.50	1
3	[bmim]Br (200)	100	94	0.46	3
4	TBACl (200)	100	96	0.51	2
5	TBABr (200)	100	74	0.54	1
6	TMABr (200)	97	95	0.65	–
7	TBAI (200)	100	96	0.52	–
8	LiCl (200)	100	92	0.60	–
9	LiI (50)	50	47	0.38	–
10	NaCl (200)	33	32	0.58	–
11	NaF (200)	1	0	–	–
12	NaBr (200)	97	92	0.52	–
13	HCl (30)	22	0	–	–

^{a} Styrene (0.2 ml, 1.75 mmol), $Ru_3(CO)_{12}$ (3.7 mg, 0.33 mol%), halide source, MeOH (3 ml), 130 °C, 10 bar, 4 h. ^{b} 1 mol% $Ru_3(CO)_{12}$.

no satisfactory results (see Online Supplementary Materials, Table S1).

Unlike most Pd carbonylation catalysts, $Ru_3(CO)_{12}$–[bmim]Br system allows performing the reaction at a fairly low CO pressure. Indeed, complete conversion and 94% esters yield were achieved at the pressure as low as 5 bar, although noticeable (5% yield) formation of ethylbenzene accompanied the process. Hydrogenation can be compressed by increasing CO pressure. However, under 30 bar the conversion decreased to 94% and esters yield reduced to 88%. Pressure has little effect on regioselectivity (Figure 1).

Temperature affects greatly on the catalyst activity. Carbonylation yield increased from 11% at 100 °C to 94% at 130 °C and then dropped with further temperature increase. We also observed rapid growth of hydrogenation activity with temperature. Regioselectivity, on the contrary, varied in a narrow range (see Figure 2).

The nature of the solvent is often an important factor affecting the reaction performance. We therefore tested a number of solvents as a reaction medium to improve the iso : n product ratio. However, no improvement in regioselectivity was achieved. Notably, the enhanced ethylbenzene formation was revealed for most of the applied solvents. Thus, neat methanol is likely the best medium for the reaction (see Table 2).

To evaluate the specific activity of the new catalytic system, we charged less amount of both $Ru_3(CO)_{12}$ and NaBr (Table 3). Decreasing amount of NaBr from 200 to 100 mol% had a slight effect on the catalytic performance (entry 3). However, further decrease to 10 mol% resulted in the considerable loss of the yield (entry 4). Reasonably high yield was achieved using 0.1 mol% $Ru_3(CO)_{12}$ (entries 2, 3). Even at 0.02 mol% $Ru_3(CO)_{12}$, the yield was 36% in 4 h (entry 5). Obviously, Br^- concentration is an important factor affecting the catalyst activity. It is known that chloride anions easily substitute some of the CO ligands in $Ru_3(CO)_{12}$.[22] These mixed carbonyls $[Ru_3(Cl)(CO)_{12-n}]^-$ ($n = 1–3$) have been postulated as an active species in alkene carbonylation.[17] We assume that bromides work similarly.

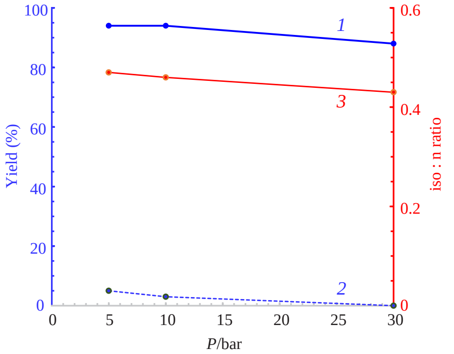


Figure 1 Effect of CO pressure on the yield of (*1*) esters, (*2*) ethylbenzene and (*3*) iso : n ratio of esters. Styrene (1.75 mmol), $Ru_3(CO)_{12}$ (0.33 mol%), [bmim]Br (200 mol%), MeOH (3 ml), 130 °C, 4 h.

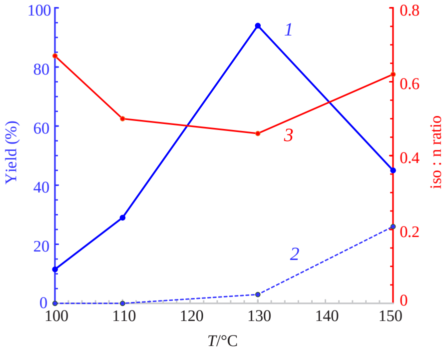


Figure 2 Effect of temperature on the yield of (*1*) esters, (*2*) ethylbenzene and (*3*) iso : n ratio of esters. Styrene (1.75 mmol), $Ru_3(CO)_{12}$ (0.33 mol%), [bmim]Br (200 mol%), MeOH (3 ml), 10 bar, 4 h.

Table 2 Effect of the solvent nature on styrene methoxycarbonylation.^{a}

Entry	Solvent	Conversion (%)	Esters		Ethylbenzene yield (%)
			yield (%)	iso : n	
1	–	100	94	0.47	5
2	1,4-Dioxane	100	81	0.51	15
3	Toluene	99	87	0.48	11
4	DMF	78	69	0.38	1
5^b	DMSO	28	18	0.60	8
6^b	PhCl	28	10	0.87	17
7^b	MeCN	77	74	0.52	–

^{a} Styrene (0.2 ml, 1.75 mmol), $Ru_3(CO)_{12}$ (3.7 mg, 0.33 mol%), [bmim]Br (767 mg, 1.75 mmol), MeOH (3 ml), solvent (1 ml), 130 °C, 5 bar, 4 h. ^{b} 0.1 mol% $Ru_3(CO)_{12}$.

Table 3 Optimization of the catalyst.^{a}

Entry	$Ru_3(CO)_{12}$ (mol%)	NaBr (mol%)	Esters		Ethylbenzene yield (%)
			yield (%)	iso : n	
1	0.33	200	92	0.52	–
2	0.1	200	85	0.48	2
3	0.1	100	89	0.49	2
4	0.1	10	37	0.61	1
5	0.02	100	36	0.76	–

^{a} Styrene (0.2 ml, 1.75 mmol), $Ru_3(CO)_{12}$, NaBr, MeOH (3 ml), 130 °C, 10 bar, 4 h.

In conclusion, Ru-catalyzed metoxycarbonylation of styrene has been systematically studied for the first time. Easily available $Ru_3(CO)_{12}$ with addition of halide promoters is very active even at low CO pressure, in contrast to most known Pd–phosphine catalysts. However, the disadvantage of the Ru catalysts is their low regioselectivity.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.11.032.

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