

The Copper–Carbon Dioxide System, a New Mild and Selective Catalyst for the Methoxylation of Non-activated Aromatic Bromides

D. Nobel

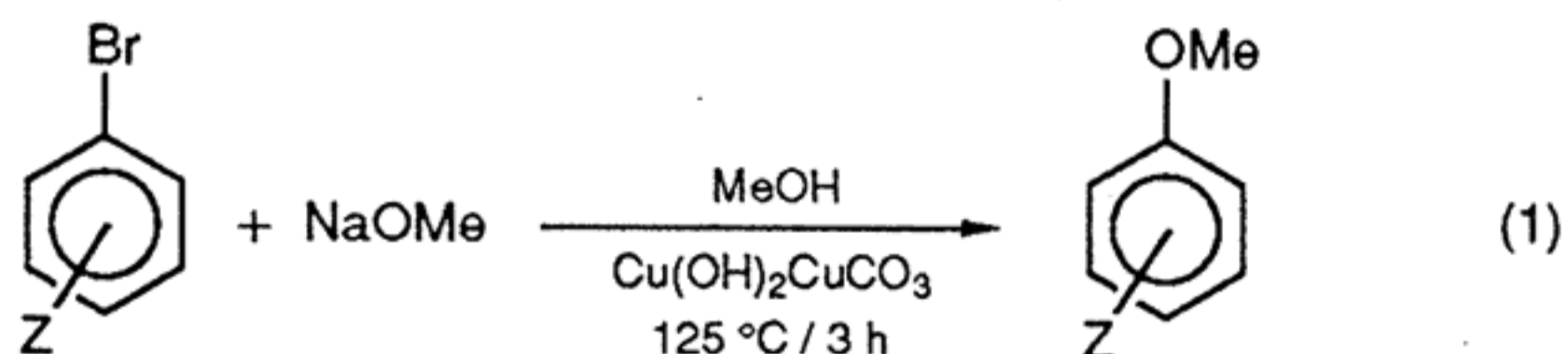
Rhône Poulenc Recherches, Centre de Recherches des Carrières, 85, avenue des Frères Perret, B.P. 62, F69192 Saint-Fons Cedex, France

Copper when associated with carbon dioxide is a mild and selective catalyst for the methoxylation of numerous non-activated aromatic bromides.

In general, aromatic nucleophilic substitution provides an attractive route to many functionalized aromatics.¹ However, a lack of selectivity, high temperatures and the requirement of solvents like hexamethylphosphorous triamide (HMPT), dimethylformamide (DMF) and pyridines, which are not consistent with current environmental awareness, characterize these reactions.²

Here, we describe a new mild and efficient catalyst for the methoxylation of bromoaromatics in methanol *i.e.* the Cu^{II}–CO₂ system, which can be used on a kilogram scale.³

The reaction of bromobenzenes with sodium methoxide in methanol in the presence of catalytic amounts of basic copper(II) carbonate is catalysed by CO₂ [see eqn. (1)].

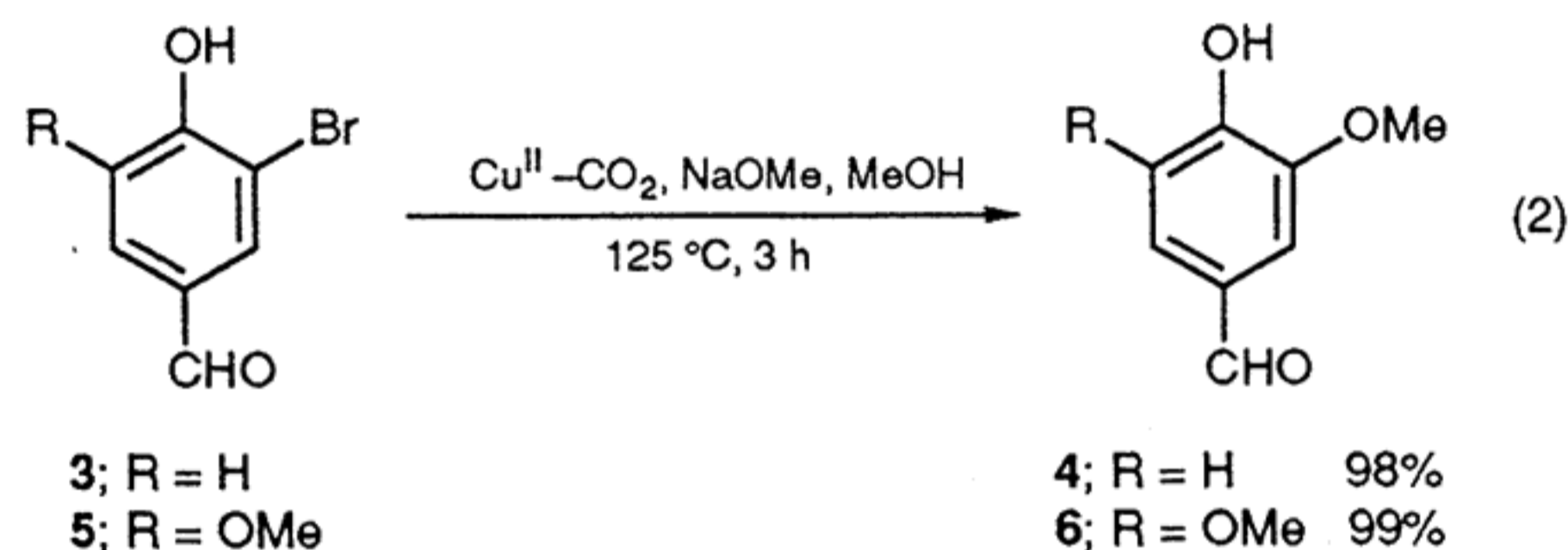


1; Z = 2 - OH	without CO ₂	39%
	with CO ₂	85%
2; Z = 4 - OH	without CO ₂	26%
	with CO ₂	70%

In a typical procedure, a mixture of the bromobenzene (10 mmol), methanol (25 ml), sodium methoxide (40 mmol) and carbon dioxide (4 mmol) was stirred for 3 h at 125 °C in a poly(tetrafluoroethylene) (PTFE) lined autoclave.

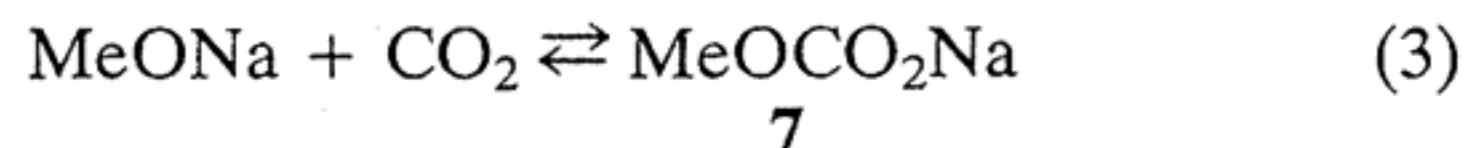
After the usual workup, the anisoles were obtained in virtually quantitative yields (Table 1). High selectivities (90–100%) were achieved; the usual coproduction of reduced benzenes could not be detected.⁴

Even aromatic aldehydes have been methoxylated without protecting the aldehydic function.⁵ Thus, vanillin **4** and syringaldehyde **6** have been prepared in quantitative yields using the CO₂–Cu^{II} system [see eqn. (2)].



However, we were unable to bring the substitution of chlorobenzene by the methoxy group to completion (yield *ca.* 4%). Reduction of copper(I) to copper metal is presumably responsible for the low yields observed.⁶

The nature and the oxidation state of the copper halide engaged are not critical since we obtained similar results with CuCl₂, CuBr₂, CuCl or CuBr. Copper concentration has only a slight kinetic effect in the 5–15% concentration range. During the course of the reaction, carbon dioxide is rapidly converted, in a carbonation reaction to monomethylcarbonate **7** [see eqn. (3)]. Separate experiments showed the equilibrium to be shifted strongly to the right, suggesting **7** to be the actual cocatalyst.



This is confirmed by the fact that the rate of the reaction is correlated to the carbonation level of sodium methylate. The catalytic effect of CO₂ is observable even at 2% carbonation

Table 1 Methoxylation of substituted bromoaromatics

Entry	Substrate	Conversion (%)	Selectivity (%)
1	Bromobenzene	100	92
2	Bromo-2-phenol	85	100
3	Bromo-4-phenol	70	100
4	Bromo-2-anisole	90	97
5	Bromo-4-anisole	94	99
6	Bromo-4-fluorobenzene	100	92
7	1,2,3-Tribromobenzene	100	65 ^a

^a The balance to 100% consists of bromo- and dibromo-anisoles.

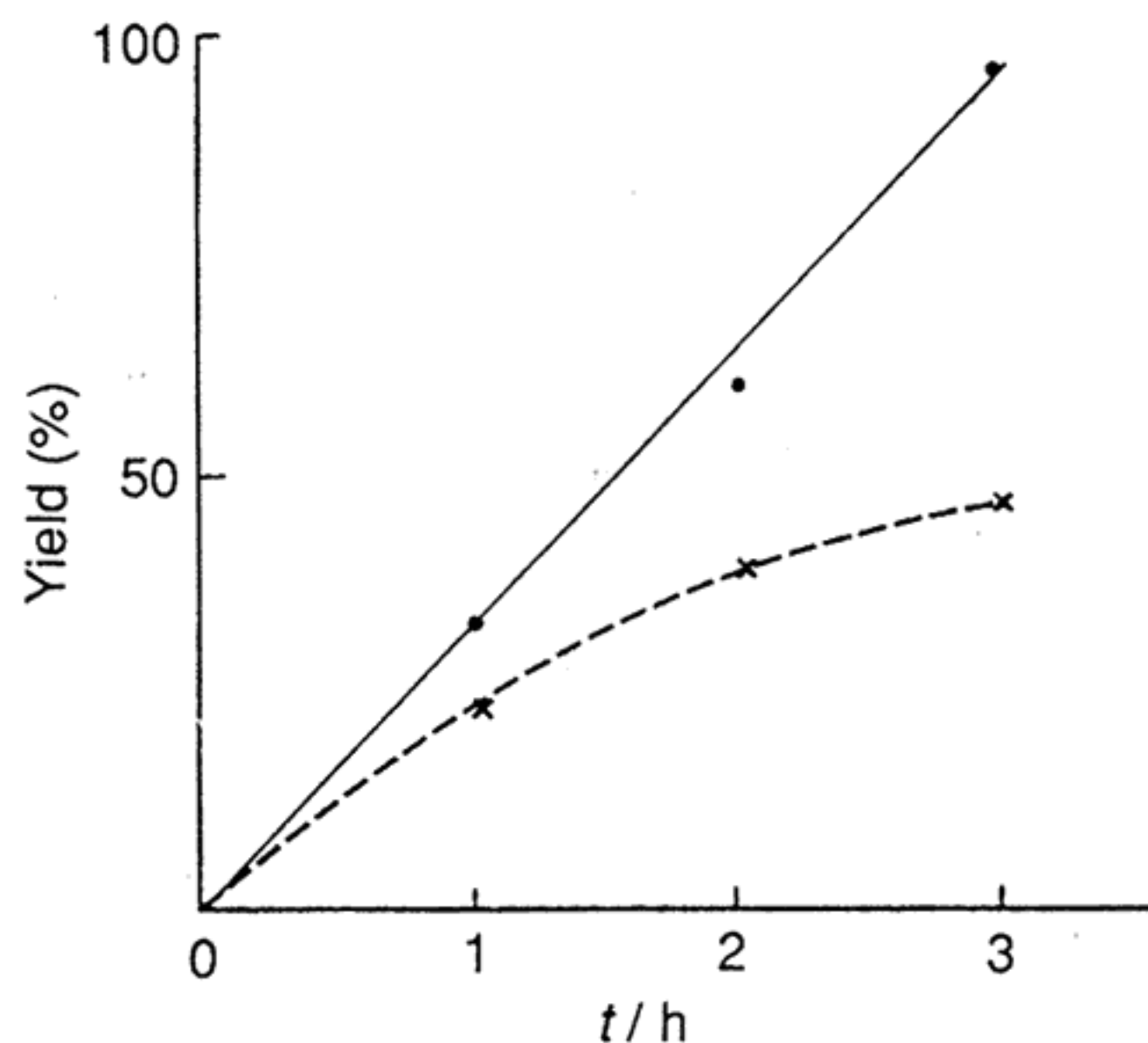


Fig. 1 Yield of **7** vs. time. Reagents and conditions: **5**, 10 mmol, NaOMe 40 mmol, MeOH 25 ml, Cu(OH)₂CuCO₃ 0.5 mmol, 125 °C –3 h; ● with CO₂ 4 mmol, × without CO₂.

and reaches its maximum at about 10%. However, replacing the sodium methoxide by pure **7** [in reaction (2)] does not afford any **4**. Thus, **7** is not a methoxide ion carrier.

Kinetic measurements performed on the reaction of eqn. (2), show the reaction rate being zero order in **5**, and,

therefore, is not involved in a rate-determining step (Fig. 1). Additional experiments to get more insight into the substitution mechanism show. (i) That isoelectronic compounds to CO₂ such as isocyanates have a similar activating effect affording comparable yields. (ii) That radical scavengers such as hydroquinone inhibit completely the reaction. 1,4-Dinitrobenzene had a similar effect when present at the beginning of the reaction but not when added once the substitution has started. (iii) That copper(II) is reduced in the presence of the methoxide ion.

These observations suggest that electron transfer occurs in the early stage of the reaction, *i.e.* the reduction of copper(II) to copper(I); but not during the substitution process. They give further support to the mechanistic pathway proposed by H. Aalten *et al.*⁷

In conclusion, solvolysis of non-activated bromoaromatics in methanol using the CO₂-Cu system affords under mild conditions the corresponding anisoles in quantitative yield. It provides an economical and environmentally acceptable process for the manufacture of substituted anisoles.

The author gratefully acknowledges Rhône-Poulenc for permission to publish this work.

Received, 14th September 1992; Com. 2/04920A

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