

The Carbonylation Reaction of Nitrobenzene to Methyl Phenylcarbamate: Highly Efficient Promoters for the Palladium–Phenanthroline Catalytic System Based on Phosphorus Acids**

Fabio Ragaini,* Carlo Cognolato, Michela Gasperini, and Sergio Cenini

Carbonylation of nitroarenes to carbamates according to Equation (1) offers a possible alternative to the current



technology, which employs the toxic phosgene.^[1–3] If the isocyanate is the desired product, this can be obtained by thermal cracking of the carbamate.

Despite intense effort from both industrial and academic laboratories, there is yet to be developed a process that can compete from an economical point of view with the established technology. This is mostly due to the insufficient turnover numbers (TONs) that even the most efficient catalysts can achieve, thus making recycling the catalyst too expensive. In recent years the catalytic system based on palladium–phenanthroline complexes has emerged as the most promising for possible industrial applications.^[4–20] Several groups have reported that the addition of acidic cocatalysts (carboxylic acids^[8,9,12,14] or phenanthroline salts^[16–18,20]) markedly improves both the rate and selectivity of the carbonylation of nitroarenes to give isocyanates or carbamates. We were intrigued by the observation by van Leeuwen et al.^[12] that there was no correlation between the acidity of the carboxylic acid employed as promoter and the increase in reaction rate. This suggested to us that a bifunctional activation process may be operative, thus as a working hypothesis, we decided to investigate the promoting activity of a series of substances that may have a superior bifunctional activation ability than carboxylic acids. It should be noted that there is presently only some preliminary mechanistic data to indicate that bifunctional activation is

[*] Prof. Dr. F. Ragaini, Dipl.-Chem. C. Cognolato, Dipl.-Chem. M. Gasperini, Prof. Dr. S. Cenini
Dipartimento di Chimica Inorganica
Metallorganica e Analitica, ISTM–CNR
and
INSTM, UdR Milano, via Venezian 21, 20133 Milano (Italy)
Fax: (+39) 02-5031-4405
E-mail: fabio.ragaini@unimi.it

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indeed occurring, however, this working hypothesis has proved fruitful in allowing a marked improvement in the efficiency of the catalytic system, in terms of both reaction rate and catalyst lifetime.

As candidates for the promotion of bifunctional activation, we initially investigated 2-hydroxypyridine,^[21] which had previously been shown by us to act as a promoter for the reaction in Equation 1 when $[\text{Rh}(\text{CO})_4]^-$ was employed as the catalyst,^[22] its 5-chloro analogue, and a phosphorus acid: diphenylphosphinic acid.^[21,23] Van Leeuwen and co-workers have reported on the promoting efficiency of carboxylic acids in conjunction with $[\text{Pd}(\text{phen})_2][\text{TfO}]_2$ (phen = 1,10-phenanthroline; $\text{TfO}^- = \text{CF}_3\text{SO}_3^-$) as a catalyst at 135 °C.^[12,14] However, in another paper,^[11] the same authors reported that the related $[\text{Pd}(\text{phen})_2][\text{BF}_4]_2$ complex affords better results. We have compared both of these complexes in the presence of the aforementioned promoters, also including benzoic acid and $[\text{phenH}][\text{PF}_6]$ for a comparison, and in a broader range of temperatures. The results are reported in Table S1 (see Supporting Information). The main conclusions that can be drawn from the data reported are the following:

- 1) We confirm that benzoic acid increases both conversion and selectivity when employed at 135 °C with $[\text{Pd}(\text{phen})_2][\text{TfO}]_2$ as catalyst. However, with the more active tetrafluoroborate catalyst, no effect on conversion is observed at either 135 or 150 °C, although an increase in selectivity is still observed. A positive effect on the reaction rate is only observed at 170 °C with $[\text{Pd}(\text{phen})_2][\text{BF}_4]_2$.
- 2) 2-Hydroxypyridine and its chlorinated analogue show some promoting effects but, at least for the triflate catalyst, the effect is smaller than that of benzoic acid and thus they were not investigated further.
- 3) Mestroni's promoter^[16–18,20] ($[\text{phenH}][\text{PF}_6]$) is also effective with the tetrafluoroborate catalyst, in accordance with the literature. Under these conditions it affords better conversions, but lower selectivities with respect to benzoic acid.
- 4) Diphenylphosphinic acid is clearly the best promoter, and increases rate and selectivity with both catalysts at all temperatures.

Working under a pressure of CO (60 bar), the reaction temperature and the amounts of phen and diphenylphosphinic acid were optimized. During the optimization study it was realized that, in accordance with data reported in the literature,^[16–20] the addition of a small amount of 2,2-dimethoxypropane as an internal drying agent has a beneficial effect on the selectivity. This optimization of the conditions allowed us to work at the unprecedented catalytic ratio $\text{PhNO}_2:\text{Pd} = 10^4$. Under these conditions, the reaction shows an induction time of about one hour, after which it proceeds with a zero-order reaction rate with respect to PhNO_2 without showing any rate decrease due to possible decomposition of the catalytic system (Figure 1). The reaction is 5.4 times slower during the first hour than at any following time. It should be noted that the autoclave takes about 15 min to reach the final temperature when immersed in the preheated oil bath (see Experimental Section), but the reaction certainly starts well before full equilibration has been achieved. However, a delay of 15 min in the first hour would, by itself,

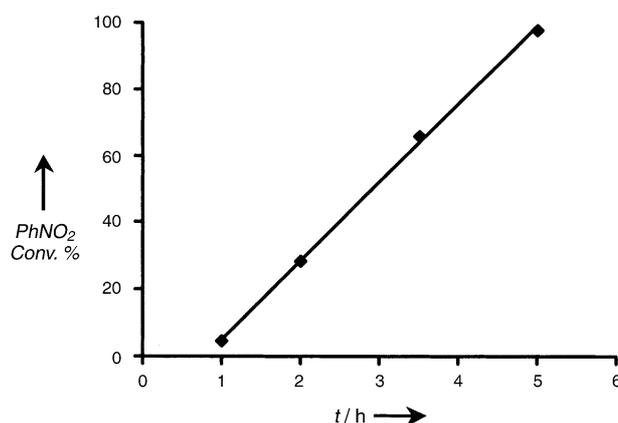


Figure 1. Dependence of PhNO_2 conversion on reaction time. Experimental conditions: $[\text{Pd}(\text{phen})_2][\text{BF}_4]_2$ (2.8 mg, 4.4×10^{-3} mmol) in methanol (30 mL) and 2,2-dimethoxypropane (1.0 mL); molar ratios $\text{Pd}/\text{phen}/\text{Ph}_2\text{POOH}/\text{PhNO}_2 = 1:100:682:10000$; $T = 170$ °C; $P_{\text{CO}} = 60$ bar. The linear regression affords a line with the equation: $\text{Conv. \%} = 23.49t - 18.56$ ($R^2 = 0.999$).

cause the reaction to be only 1.3 times slower in the first hour than in the following time.

Since aniline is known to be formed as an intermediate in several catalytic carbonylation reactions of nitroarenes,^[1–3,15] we investigated the effect of its addition from the beginning of such reactions. As shown in Table S2 (see Supporting Information), the addition of aniline (4% with respect to the starting nitrobenzene) accelerates the reaction in the first hour by a factor of approximately four. Thus it is clear that the induction time is, for the most part, due to the required generation of aniline, which is slow in the dry solvent employed. The addition of an equimolar amount of aniline with respect to nitrobenzene has been previously reported to accelerate the rate of the reaction with a palladium–phenanthroline catalyst,^[13] but in the presence of such an high amount of aniline the selectivity of the reaction is much decreased and large amounts of azoxybenzene were formed.

At this stage other phosphorus acids were tested. A comparison of the data in Table 1 shows that the introduction of an electron-donating group on the phenyl rings of diphenylphosphinic acid has a small positive effect, but the electron-withdrawing chloride is not tolerated. Phenylphosphonic acid and its substituted analogues are a better class of promoters, but phenylphosphonic acid, which can act as a reductant towards palladium, completely deactivated the catalytic system, apparently because of the fast formation of inactive palladium metal. Even the more acidic dithiodiphenylphosphinic acid was not a suitable promoter, and it is noted that this acid is known not to be a good bifunctional catalyst.^[21] However, it was very interesting to observe that the best conversion was obtained with commercial 85% phosphoric acid! This is an ideal promoter in terms of cost, absence of toxicity, and ease of separation from the reaction products. The 1:1 mixture of mono- and dimethylphosphate, obtained by reaction of P_4O_{10} with the stoichiometric amount of methanol, was less efficient, but still retained a high promoting efficiency, which shows that a partial esterification of the acid does not block catalytic activity. Such esterification

Table 1: Comparison of different phosphorus promoters.^[a]

Promoter	Promoter/Pd molar ratio	PhNO ₂ conv. % ^[b]	PhNHCO ₂ Me selectivity [%] ^[c]	PhNH ₂ selectivity [%] ^[c]	PhN(O)=NPh selectivity [%] ^[c]
–	–	4.6	13.7 (11.0) ^[d]	– ^[d]	51.0
Ph ₂ POOH	682	37.0	89.5 (87.9) ^[d]	– ^[d]	1.8
(4-MeC ₆ H ₄) ₂ POOH	682	37.8	93.3 (91.7) ^[d]	– ^[d]	1.9
(4-ClC ₆ H ₄) ₂ POOH	682	7.7	64.0 (60.3) ^[d]	– ^[d]	–
PhPO(OH) ₂	682	42.5	86.8	<0.1	1.6
4-MeC ₆ H ₄ PO(OH) ₂	682	49.2	90.3	0.4	1.6
4-ClC ₆ H ₄ PO(OH) ₂	682	34.6	86.4	0.7	2.1
Ph ₂ PSSH	682	–	–	–	–
PhPH(O)OH	682	–	–	–	–
H ₃ PO ₄ (100%)	682	42.6	93.5	2.8	–
H ₃ PO ₄ (100%)	753	47.9	89.0	0.9	–
H ₃ PO ₄ (85%)	682	55.1	87.1	3.0	1.7
OP(OMe)(OH) ₂ / OP(OMe) ₂ (OH) 1:1	682	33.4	85.4 (84.0) ^[d]	– ^[d]	<1
PhCOOH	682	17.1	83.6 (77.3) ^[d]	– ^[d]	18.6
[phenH][PF ₆]	227	10.6	83.8 (81.3) ^[d]	– ^[d]	–

[a] Experimental conditions: [Pd(phen)₂][BF₄]₂ (1.4 mg, 2.2 × 10⁻³ mmol) in methanol (15 mL) and 2,2-dimethoxypropane (0.5 mL) for 1.5 h; molar ratio Pd/phen/PhNH₂/PhNO₂ = 1:100:200:7500; P_{CO} = 60 bar. [b] Calculated with respect to the starting amount of PhNO₂. [c] Calculated with respect to the converted PhNO₂. Aniline selectivity is calculated considering only the excess amount of aniline compared with the initial quantity. Most of the remaining mass balance is due to diphenylurea, which was observed, but not quantified by GC. Azobenzene was below or very close to the detection limit (0.1%). [d] Less aniline was found at the end of the reaction, as compared with the initial amount. The values in parentheses refer to the selectivity in terms of the total PhNO₂ and PhNH₂ that had reacted.

does indeed occur during the reaction, but to a small extent. Under the conditions described in Table 1, but for a longer time (6 h), 32% of the added phenylphosphonic acid was transformed into the monomethyl ester and no diester was detectable by ³¹P NMR spectroscopy. The esterification is a purely organic transformation and essentially the same amount of monoester (30%) is obtained under similar conditions in the absence of the metal and nitrobenzene.

The influence of CO was investigated employing 85% phosphoric acid as the promoter. The reaction is clearly first order with respect to CO pressure (Figure 2). Because of

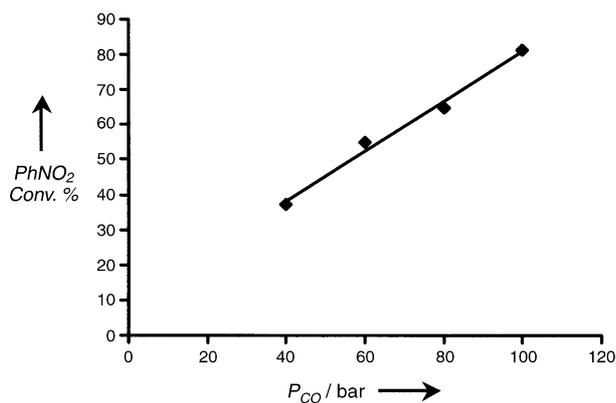


Figure 2. Influence of CO pressure on PhNO₂ conversion. Experimental conditions: [Pd(phen)₂][BF₄]₂ (1.4 mg, 2.2 × 10⁻³ mmol) in methanol (15 mL) and 2,2-dimethoxypropane (0.5 mL) for 1 h; molar ratio Pd/phen/H₃PO₄/PhNH₂/PhNO₂ = 1:100:682:200:7500; T = 170 °C. The linear regression affords a line with the equation: Conv. % = 0.713 P_{CO} + 9.69 (R² = 0.989).

technical limits, we could not investigate initial pressures higher than 100 bar, but these should afford even better results. By working at the conditions described in Table 1, but at 100 bar, we obtained a 81.2% conversion (with a 87.5% selectivity), corresponding to a turnover frequency (TOF) of almost 6000 h⁻¹. The highest value previously reported in the literature for the carbonylation reaction of nitrobenzene to afford methyl phenylcarbamate is 960 h⁻¹.^[19] The catalytic system is very stable, and by decreasing the amount of palladium we could obtain an unprecedented 10⁵ turnovers in 24 h, albeit with a somewhat lower selectivity (77.5%),^[24] which approaches the limit for which a commercial application can be considered.

In conclusion, we have found an improved catalytic system for the carbonylation of nitrobenzene that for the first time yields activities and catalyst lifetimes in the

range necessary for industrial applications. Preliminary results indicate that the improved features also apply to the economically very important dinitrotoluenes. Optimization of the experimental conditions with these substrates is in progress.

Experimental Section

In a typical catalytic reaction the catalyst, phen, PhNO₂, PhNH₂, and the acidic promoter were weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide neck under dinitrogen, which was then cooled to -78 °C, evacuated, and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap that contained glass wool that allows gaseous reagents to exchange. The flask was rapidly transferred to a 200 mL stainless steel autoclave with a magnetic stirrer. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure and the autoclave was immersed in an oil bath preheated to the required temperature; the autoclave took about 15 min to fully equilibrate at the final temperature. Other experimental conditions are reported in the legends of the tables and figures. At the end of the reaction the autoclave was cooled with an ice bath, vented, and the products were analyzed by gas chromatography (with naphthalene as an internal standard).

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