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α-Arylation of diethyl malonate via enolate with bases in a heterogeneous phase

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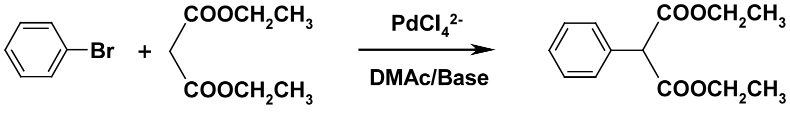
Abstract—The influence of various heterogeneous bases on yield and selectivity in the α-arylation of diethyl malonate was studied. Barium hydroxide was found to provide excellent results in this context. The bases used can be easily removed from the reaction medium by filtration. © 2002 Elsevier Science Ltd. All rights reserved.

Carbon–carbon coupling techniques are of special interest for the production of fine chemicals. Palladium is the most flexible and widely used metal for this purpose. In fact, Pd has been used in Heck,[1,2] carbonylation[3,4] and arylation reactions.[5,6] Specifically, this metal has received special attention in recent years as a catalyst for the preparation of α-arylcarbonyl compounds; also, a large number of arylation reagents have been reported which, however, are of limited interest as they must be specific for the particular α-arylcarbonyl compound.

This paper reports the results obtained in the direct arylation of carbonyl compounds via an enolate species using a palladium catalyst and a base in a heterogenous phase. This procedure improves on existing alternatives as the base can be removed from the medium simply by filtration once the reaction is finished. We used the arylation of diethyl malonate with bromobenzene as model reaction (Scheme 1), sodium tetrachloropalladate as catalyst and *N*,*N*-dimethylacetamide (DMAc) as solvent, as well as various solid bases to obtain the enolate form. The solids tested had previously been successfully used in a number of organic processes involving carbanions.[7–10] The authors themselves have employed some, which they have characterized as regards structural and surface properties,[9–12] in the last few years. In this work, a heterogenous solid of this type was for the first time used instead of the homogenous bases (metal alkoxides preferentially) usually employed for this purpose.

Diethyl malonate was chosen as reactant on the grounds of its symmetry; this facilitates the analysis of its reaction products, which possess no regioisomers.

In the literature, the palladium-catalyzed arylation of carbonyl compounds is described as a carbon–carbon coupling reaction between an aryl halide and an enolate (Scheme 2) that takes place in situ in the presence of an appropriate base.[6] As noted earlier, this initial work focussed on the influence of the base on conversion and selectivity in the process. To this end, we tested various solids containing surface basic groups. Table 1 shows the conversion and selectivity results obtained in the reaction of bromobenzene with diethyl malonate. As can be seen, with the exception of three solids (entries 7, 8 and 9 in Table 1), all bases provided rather poor diethyl phenylmalonate yields as they were unable to form the enolate of diethyl malonate to an adequate extent; this resulted in a poor yield in the subsequent



Scheme 1. The α-arylation process studied.

Keywords: coupled reactions; Pd catalyst; arylation; diethyl malonate.

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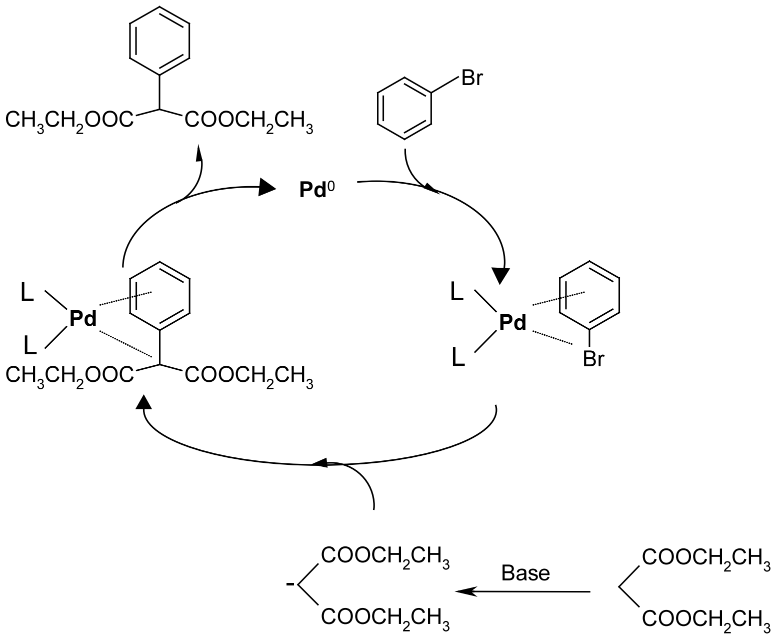

Scheme 2. Proposed reaction pathway for the Pd-catalysed α-arylation of carbonyl compounds (as applied to the reaction between diethyl malonate and bromobenzene).

Table 1. Results obtained in the arylation of diethyl malonate with bromobenzene using Na_2PdCl_4 as catalyst and various heterogeneous bases[a]

Entry	Base/catalyst	Yield GC (%)[b]	Selectivity (%)[c]
1	MgO/Al_2O_3	16.5	92
2	MgO/Ga_2O_3	8.3	87
3	MgO/CaO	6.5	89
4	MgO	6.0	93
5	$Ca(OH)_2$	96.1	94
6	$Ba(OH)_2$	99.0	97
7	K_2CO_3	93.1	94
8	Na_2CO_3	41.7	91
9	Li_2CO_3	14.3	92
10	Blank-1[d]	No reaction	–
11	Blank-2[e]	No reaction	–

[a] Reaction conditions: 10 mmol diethyl malonate, 15 mmol bromobenzene, 2% mol Pd, 20 mmol base, 6 mL DMAc.

[b] Diethyl phenylmalonate yield at 24 h of reaction (20 and 14 h for entries 5 and 6, respectively).

[c] Selectivity towards diethyl phenylmalonate.

[d] Blank containing no base.

[e] Blank containing no palladium.

carbon–carbon coupling reaction. This outcome may have been the result of the solids used only being effective carbanion-forming agents at higher temperatures. In fact, most reported carbanionic processes involving these solids take place at temperatures above 300°C and our reactions were conducted at only 100°C. However, as stated above, both calcium and barium hydroxide, and potassium carbonate, gave good yield and selectivity results (particularly barium hydroxide, which provided conversions near 100% after 14 h of reaction).

Table 2. Results obtained in the arylation of diethyl malonate with arylbenzenes using Na_2PdCl_4 and $Ba(OH)_2$ as catalysts

X-Benzene	Yield (%)	Selectivity (%)
Iodobenzene	100	98
Bromobenzene	99	97
Chlorobenzene	93	97

Once $Ba(OH)_2$ was found to be the solid providing the best results, we used it in the reaction of other arylbenzenes. Table 2 shows the results obtained; as can be seen, both yield and selectivity were excellent for the three arylbenzenes studied.

In summary, the combined use of a heterogeneous base and a homogeneous catalyst provides extremely good results in the α-arylation of diethyl malonate. Work currently in progress is being focussed on the preparation of products of interest to various chemical industries (foods, perfumes) using this procedure and on the heterogenization of the homogeneous catalytic step with a view to advancing further in the separation of the reaction products.

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