ORGANIC LETTERS

2012
Vol. 14, No. 8
2188–2190

Synthesis of Water-Soluble Phosphine Oxides by Pd/C-Catalyzed P–C Coupling in Water

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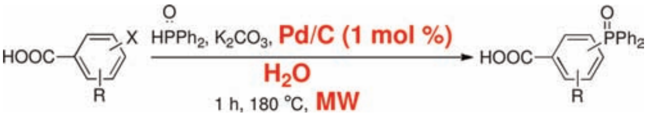
Received March 7, 2012

ABSTRACT



Cross-coupling between diphenylphosphine oxide and halogenated benzoic acids catalyzed by Pd/C in water is a green, simple, and fast protocol to obtain water-soluble tertiary phosphine oxides without the addition of ligands and additives. Low reaction times and microwave irradiation make this method general and excellent for laboratory and large-scale synthesis without the need to use organic solvents in reactions and workup.

Phosphine oxides are important intermediates for chemical synthesis because they are precursors to free phosphines, which are essential for transition metal catalysis[1] and for organocatalysis.[2] They can also be excellent ligands[3] and have found application in organocatalysis based on their Lewis basic properties.[4] Water-soluble phosphines and phosphine oxides have special advantages in industrial processes based on homogeneous catalysts since they allow easier separation of the metal catalyst from the reaction mixture by using two-phase water/organic solvent systems.[5] The SHELL Higher Olefinic Process (SHOP) is a practical industrial example of a successful application of water-soluble phosphines in two-phase homogeneous catalysis.[6]

The introduction of polar groups, such as sulphates, ammonium salts, and carboxylates, to organophosphorous compounds is however strongly limited by the few methods available in the literature, which usually require either harsh conditions or the use of air-sensitive reagents in stoichiometric amounts.[5a] Catalytic processes that build phosphorus–carbon bonds (P–C coupling)[7] based on Pd,[8] Cu,[9] and Ni[10] overcome some of these limitations and allow the synthesis of phosphines under mild conditions

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and with great functional group tolerance. Still, P–C coupling reactions are mostly homogeneous systems that need (a) the presence of ligands that are able to activate bromo or possibly chloroaryl/allyl derivatives, (b) the use of high boiling organic solvents, (c) generally secondary phosphines as coupling partners, which are oxygen-sensitive reactants, and (d) quite long reaction times up to 48 h to give good conversion. For the reasons mentioned above, P–C couplings are still limited even though they present major advantages over traditional stoichiometric methods.

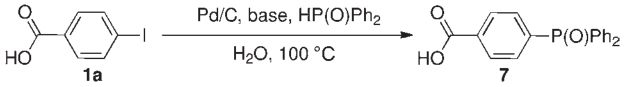
A catalytic method of industrial applicability that produces water-soluble phosphine derivatives should ideally be (a) insensitive to air, (b) recyclable, (c) sustainable from an environmental point of view, (d) versatile, and (e) potentially scalable. We present here a method to achieve P–C coupling with such characteristics. This method produces water-soluble phosphine oxides with carboxylic acid groups by employing diphenlyphosphine oxide as the P-source and Pd/C as the catalyst. Since our interest is to produce water-soluble phosphorus compounds, H_2O is the obvious choice as the reaction medium for both reaction and workup. Sustainability and nontoxicity are key points for this new evironmentally friendly process.

Secondary phosphine oxides are known to react with bromo aryls, allyls, and aryltriflates in the presence of a Pd,[11] Ni,[10] or Cu[12] source and a base in organic solvents. Recently, Zhang et al. published a P–C coupling of a bromo- and iodoaryl with diphenylphosphine oxide ($HP(O)Ph_2$) in water using a nickel/zinc homogeneous system.[13] No heterogeneous catalytic systems that produce phosphine oxides from P–C coupling are known, to the best of our knowledge.

An initial screening was performed with 4-iodobenzoic acid, which was used as a model reactant for coupling with diphenylphosphine oxide catalyzed by Pd/C in water using conventional heating. The screening results of temperature, different bases, phase-transfer additives, and time are shown in Table 1.

When the reaction was performed at temperatures below 100 °C, no conversion was observed (entry 2). The base had a strong influence on the conversion, and K_2CO_3 was found to be best among Na_2CO_3, NaOH, and Et_3N (entries 1 and 3–5). Although initial screening was performed in the presence of a phase transfer agent such as tetra-butylammonium bromide (TBAB), we discovered that it did not have any positive effects on the reaction (entries 8, 9). Furthermore, a slight excess of $HP(O)Ph_2$ was needed to obtain full conversion (entries 8, 9). Under optimized conditions, 4-iodobenzoic acid (0.55 mmol) was dissolved in degassed water (5 mL) with Pd/C (1 mol %), K_2CO_3 (2.2 mmol), and $HP(O)Ph_2$ (0.72 mmol), and the mixture was stirred at 100 °C for 1 h (entry 9). After filtration over Celite of the catalyst, the filtrate was simply acidified with HCl (~1 M), and the product was recovered by filtration. No organic solvent was used.

Table 1. Initial Screening of P–C Coupling of 4-Iodobenzoic Acid under Conventional Heating[a]



entry	Pd/C (mol %)	$HP(O)Ph_2$ (equiv)	base (mol %)	TBAB (equiv)	conversion (%)
1	5.0	1.0	Na_2CO_3 (6 equiv)	1.0	62
2[b]	5.0	1.0	Na_2CO_3 (6 equiv)	1.0	0
3	5.0	1.0	Et_3N (6 equiv)	1.0	58
4	5.0	1.0	NaOH (6 equiv)	1.0	80
5	5.0	1.0	K_2CO_3 (6 equiv)	1.0	85
6	0.20	1.0	K_2CO_3 (6 equiv)	1.0	44
7	1.0	1.0	K_2CO_3 (6 equiv)	1.0	87
8	1.0	1.3	K_2CO_3 (6 equiv)	–	98
9[c]	1.0	1.3	K_2CO_3 (4 equiv)	–	99

[a] Standard conditions: iodobenzoic acid (0.55 mmol), $HP(O)Ph_2$, base, Pd/C, H_2O (10 mL), conventional heating, 100 °C, 1 h. [b] Reaction temperature: 70 °C. [c] H_2O (5 mL).

Different halogenated benzoic acids (4-bromo and 2-iodobenzoic acid) did not yield the desired product under conventional heating. This limited the scope of the reaction. We therefore used microwave (MW) heating, instead of conventional heating, inspired by the results of Stadler et al. in the case of P–C coupling with diphenylphosphine.[14] Figure 1 summarizes different substrates and their yields.

Simple iodo- and bromobenzoic acids such as 3- and 4-bromobenzoic acid (**1a** and **2a**) and 3- and 4-iodobenzoic acid (**1b** and **2b**) readily coupled with $HP(O)Ph_2$ in high yields at 180 °C under MW irradiation, to give phosphine oxides **7** and **8**. Iodo derivatives yielded less product, due to their easier tendency to dehalogenate under reaction conditions as observed in other similar protocols.[15,11c] Traces of benzoic acid were observed via ^1H NMR spectroscopy of the crude reaction mixture. 4-Chlorobenzoic acid also coupled with $HP(O)Ph_2$, although in 18% yield.

Commercially available 3-bromo-4-methylbenzoic acid (**3a**) and 3-iodo-4-methylbenzoic acid (**3b**) gave the corresponding novel phosphine oxide **9** in 60% and 81% yield, respectively. Phosphine oxide **10** was produced in moderate yield from 3-bromo-4-methoxybenzoic (**4a**) and

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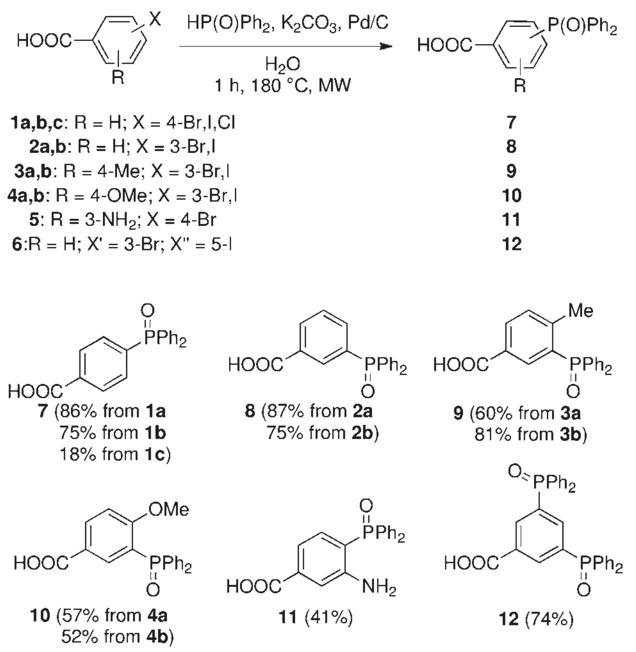

Figure 1. P–C coupling of several halogenated benzoic acids under MW heating. Standard conditions: halogenated benzoic acid (1.1 mmol), $HP(O)Ph_2$ (1.4 mmol), K_2CO_3 (4.4 mmol), Pd/C (0.011 mmol), H_2O (10 mL), MW irradiation, 180 °C, 1 h.

3-iodo-4-methoxybenzoic acid (**4b**). ^{1}H NMR spectroscopic analysis of the reaction mixture revealed that the moderate yield was due to dehalogenation in the case of **4b**[15,11c] and due to both low conversion and dehalogenation in the case of **4a**. The novel phosphine oxide-amino (**11**) and bis(phosphine oxide) (**12**) compounds were also synthesized in 41% and 74% yield, respectively, from commercially available starting materials **5** and **6**. All substrates with a halogen in the 2-position gave only traces of product due to steric hindrance. Halogenated hydroxybenzoic acids gave only traces of product under the given reaction conditions.

The workup was performed by filtration over Celite of the catalyst, acidification, and filtration of the product, as described above. ^{31}P and ^{1}H NMR spectroscopy analysis of the crude reaction mixture revealed the presence of a phosphorus-containing byproduct, which was identified as diphenylphosphinic acid.[16] Nevertheless, such a byproduct was easily removed by acidification of the reaction mixture at controlled pH between 4 and 5. Under such conditions, the product precipitated, whereas diphenylphosphonic acid, residual starting material, and dehalogenated product remained in solution. Alternatively, starting material and dehalogenation product were removed from the precipitate by sublimation. Besides **12**, which was recrystallized in ethanol/water, all the phosphine oxides herein reported could be isolated with >95% purity[17] without the employment of organic solvents.

We also tested the recyclability of the catalyst for the phosphination of substrate **3b**. After the first run, the catalyst was filtered with a microfiber glass filter and reused at 180 °C under MW irradiation. The second catalyst run produced **9** in 78% yield, comparable to the first run. Pd/C as recyclable catalyst for P–C coupling is not unprecedented,[14,18] and its catalytic activity is presumably due to microwaves, which create electric discharge or hot spots within the heterogeneous catalyst and are able to create small and locally superheated, highly active sites. This phenomenon has been observed and studied only in C–C coupling,[19] but analogous assumptions can be made for the P–C one.

We have developed a novel method to couple various iodo- and bromobenzoic acids with diphenylphosphine oxide in water, by using a heterogeneous and recyclable catalyst. Because of the utilization of (a) water as solvent for both reaction and workup, (b) a heterogeneous catalyst, and (c) microwave irradiation, it is an environmentally friendly and sustainable reaction for carbon–phosphorus coupling. This protocol allows the synthesis of four new phosphine oxides. The corresponding free phosphines containing carboxylic acid functionalities can be synthesized by reduction with trichlorosilane as previously described.[20] All the products were fully characterized and can be of further use as ligands for biphasic and water-soluble metal catalysis and organocatalysis. This, in combination with the easy, fast reaction, simple workup, and high purity of the desired compound, makes this reaction protocol a good candidate for application in both laboratory and large-scale synthesis.

Acknowledgment. This work was supported by the Laboratory for Catalysis and Sustainable Chemistry (LSK) at Paul Scherrer Institute, Villigen, Switzerland and by ETH Zurich, Switzerland.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.