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Rapid Formation of Triarylphosphines by Microwave-Assisted Transition Metal-Catalyzed C–P Cross-Coupling Reactions

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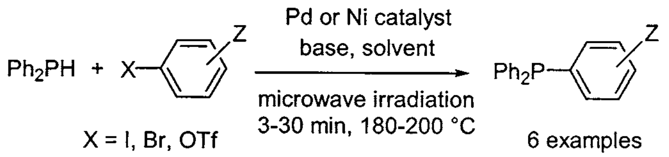
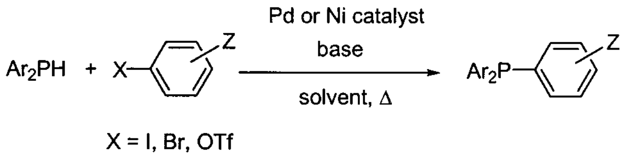
ABSTRACT



Rapid, direct transition metal-catalyzed C–P(III) cross-coupling reactions were performed by microwave dielectric heating, employing diphenylphosphine and aryl halides/triflates as substrates. Depending on the specific aryl halide/triflate precursor, the highest yields were obtained utilizing heterogeneous or homogeneous Pd or Ni catalysts in DMF or NMP in the presence of KOAc or DABCO as a base.

Tertiary phosphines are very important types of ligands in transition metal-catalyzed reactions. Among the various methods for the synthesis of such phosphine ligands, direct carbon−phosphorus (C−P) bond formation via transition metal-catalyzed cross-coupling of unprotected secondary phosphines with aryl halides/triflates can be considered as one of the most valuable procedures (Scheme 1).[1−6] In contrast to most other C−P bond-forming protocols, no introduction of protection groups at phosphorus is required for this one-pot tertiary phosphine synthesis and the method is compatible with a variety of functional groups.[1] The first successful Pd-catalyzed couplings of aryl iodides/bromides with diarylphosphines were reported by Stelzer and coworkers in 1996.[2] Similarly, a group from Merck disclosed the use of a Ni catalyst for the direct phosphination of aryl triflates with diphenylphosphine, a procedure that was applied to the preparation of the diphosphine ligand 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP).[3] Since then, a number of related protocols based on the Stelzer or Merck C−P coupling methods have been developed, making a number of functionalized triarylphosphine ligands accessible

Scheme 1



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by this route.[1,4−6] All of these protocols utilize a homogeneous transition metal catalyst and a base and generally require many hours of reaction time at high temperatures or otherwise impractical or complex synthetic manipulations (the synthesis of BINAP using the Merck protocol, for example, requires multiple addition of reagents and 2−3 days reaction time at 100 °C under an inert atmosphere).[3]

In the past few years, the utilization of microwave heating in transition metal-catalyzed transformations has attracted considerable interest.[7] Many Pd- or Mo-catalyzed reactions that typically need hours or days to reach completion with conventional heating can be brought to full conversion in only minutes utilizing microwave heating. Microwave-mediated protocols in this area include the formation of a variety of carbon−carbon as well as carbon−heteroatom bond systems, utilizing, for example, Heck, Suzuki, Stille, Sonogashira, Negishi, and Buchwald−Hartwig chemistry.[7] To the best of our knowledge, however, transition metal-catalyzed C−P(III) bond formations utilizing high-speed microwave chemistry have not been described. Herein we report our preliminary investigations on rapid, homogeneous and heterogeneous Pd- and Ni-catalyzed C−P couplings involving aryl halides/triflates and diphenylphosphine.

The conventional coupling protocols involving iodo- and bromobenzenes and secondary phosphines, reported by Stelzer and co-workers,[2] employ a variety of homogeneous Pd catalysts, base, and solvent combinations. These reactions typically furnish moderate to good yields of triarylphosphine products for iodo precursors, involving 1−72 h of heating at temperatures of 70−130 °C. The corresponding aryl bromides, however, require considerably longer times (125−130 °C for 5−7 days).[2] Initially, we tried to adapt these protocols to controlled microwave heating conditions in closed vessels,[8] using the reported MeCN/$Pd(OAc)_2$ or DMA/$Pd(Ph_3P)_4$ conditions, in the presence of different bases such as KOAc or triethylamine. Our first experiments utilized iodobenzene and diphenylphosphine as substrates (Scheme 1, X = I, Z = H, Ar = Ph). To our disappointment, we were unable to obtain reasonable yields of triphenylphosphine product utilizing either DMA or MeCN as a solvent under microwave conditions. The yield of triphenylphosphine could not be raised to >15%, and a number of unidentified byproducts were present in the reaction mixture under the high-temperature microwave conditions. After some experimentation with a variety of other solvents (DMF, NMP, toluene, dioxane), we found that NMP was a very suitable solvent for this type of transition metal-catalyzed process. NMP has considerably higher stability than, e.g., DMF, under microwave irradiation conditions,[9] absorbs microwave energy efficiently, and allows product isolation by simply pouring the reaction mixture into water. Optimized reaction conditions utilized combinations of NMP, KOAc, and 2.5 mol % of $Pd(OAc)_2$ as catalyst (Table 1). A 50% excess of iodobenzene was found to give the best yields (entries 5−8). Within 20 min, a conversion of >90% was achieved at 180−200 °C (entries 6 and 7). At higher temperatures, decomposition of the Pd(II) catalyst was observed, resulting in lower isolated product yields (entry 8) and in the deposition of a very thin black film of Pd on the microwave process vial (see below). Note that the use of $Pd(Ph_3P)_4$ as phosphine-containing homogeneous Pd catalyst as reported by Stelzer and co-workers[2] did not result in an increased product yield. Therefore, a self-replicating, ligand-generating catalyst system does not seem to be in operation here.[4]

Table 1. Microwave-Enhanced Synthesis of Triphenylphosphine from Iodobenzene and Diphenylphosphine Using $Pd(OAc)_2$ as a Homogeneous Catalyst[a]

entry	PhI (mmol)	temp (°C)	time (min)	yield (%)
1	0.50	200	10	44
2	0.50	200	20	48
3	0.60	180	10	65
4	0.60	180	20	83
5	0.75	160	20	88
6	0.75	180	20	90
7	0.75	200	20	92
8	0.75	220	20	67

[a] Reactions were carried out in NMP (1.0 mL) with 0.50 mmol of Ph_2PH in the presence of KOAc (0.50 mmol) and $Pd(OAc)_2$ (2.5 mol %, 2.8 mg). For details, see Supporting Information.

Interestingly, we discovered that it was also possible to use heterogeneous Pd sources as catalysts in these transformations. We are not aware of any literature precedent for C−P coupling reactions involving secondary phosphines catalyzed by a heterogeneous transition metal source. To our surprise, 5% Pd on charcoal (Pd/C) turned out to be a very effective catalyst for this reaction. Even small amounts of the catalyst (<1.0 mol % Pd) proved to be effective at 190−200 °C in allowing near quantitative conversions to triphenylphosphine within only 2 min (Table 2, entries 3−5). Presumably, solid Pd/C is absorbing microwave energy very

Table 2. Microwave-Enhanced Synthesis of Triphenylphosphine from Iodobenzene and Diphenylphosphine Using Pd/C as a Heterogeneous Catalyst[a]

entry	PhI (mmol)	5% Pd/C (mg)	temp (°C)	time (min)	yield (%)
1	0.50	10	190	3	76
2	0.60	10	190	3	93
3	0.75	20	190	3	98
4	0.75	20	200	3	96
5	0.75	20	200	2	96

[a] Reactions were carried in DMF (1.0 mL) with 0.50 mmol of Ph_2PH in the presence of KOAc (0.50 mmol). For details, see Supporting Information.

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(7) For a very recent review, see the following: Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.

(8) All microwave irradiation experiments were performed using the SmithSynthesizer from Personal Chemistry AB. For a detailed description of this instrument, see the following: Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630.

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efficiently and thereby acting as a locally superheated, highly active catalyst.[10] Note that here DMF proved to be a superior solvent to NMP. Evidently, because of the very short reaction times, the decomposition of DMF resulting in unwanted side-reactions is not a problem.[9] After the reaction was completed, the triphenylphosphine product could simply be isolated after filtration from the catalyst and precipitation with water. An even easier protocol was developed by using a Pd-doped microwave process vial generated by high-temperature decomposition of a soluble Pd source (see above). Here the deposited Pd on the inner glass surface was used as a catalyst, albeit the catalytic activity was found to be somewhat lower than that using Pd on charcoal (85% yield of triphenylphosphine after 3 min of microwave irradiation to 200 °C). However, these vials could be reused several times without loss of catalytic activity, eliminating the necessity of a filtration step in the workup.[11]

The above homogeneous and heterogeneous C−P coupling protocols involving iodobenzene were also applied to a number of substituted aryl iodides (Scheme 1: $Z = 2\text{-}CO_2H$, $Z = 2\text{-Br}$, $Z = 3\text{-OMe}$, $Z = 2\text{-}NH_2$ and 1-iodonaphthalene) providing the corresponding functionalized triarylphosphines in 26−86% yield (Table 3).

Table 3. Phosphine Derivatives by Heterogeneous or Homogeneous Pd Catalysis from Iodobenzene Analogs[a,b]

entry	substrate	catalyst[c]	temp (°C)	time (min)	yield (%)
1	1-iodonaphthalene	A	180	5	86
2	1-iodo-2-bromobenzene	A	200	10	74
3	3-iodoanisol	B	180	15	34
4	2-iodoaniline	C	180	20	43
5	2-iodobenzoic acid	B	180	10	26

[a] Yields not optimized. [b] All products were identified on the basis of their MS and NMR data and comparison with literature data. [c] A = 1.0 mol % Pd/C (5%), B = 2.0 mol % Pd/C (5%), C = 3.5 mol % $Pd(PPh_3)_4$.

Having established the feasibility of rapid, direct C−P cross-couplings of aryl iodides with diphenylphosphine, we were also interested to utilize aryl bromides or triflates in these processes. Due to the lower reactivity of bromobenzenes as compared to iodobenzenes, rather long reaction times were typically required for the coupling with diphenylphosphine using conventional thermal heating (5−7 days, 125−130 °C).[2] While the use of a heterogeneous Pd source such as Pd/C produced only trace amounts of triphenylphosphine under microwave irradiation conditions, we found that successful couplings could be achieved employing thermally stable homogeneous Pd catalysts, such as Herrmann's catalyst.[12] After some optimization work, we found that a 59% isolated yield of pure triphenylphosphine could be obtained exposing an equimolar mixture of bromobenzene, diphenylphosphine, and KOAc (0.50 mmol) in DMF (1.0 mL) containing 2 mol % of Herrmann's palladacycle catalyst to microwave irradiation at 180 °C for 30 min in a sealed process vial (see Supporting Information for details).

Finally, we have studied C−P coupling reactions involving phenyl triflate as a model substrate. Here we have utilized a combination of a Ni catalyst and a tertiary amine base as suggested in the literature for related C−P coupling reactions.[3] Microwave irradiation for 20 min at 180 °C of a mixture of diphenylphosphine (0.50 mmol), phenyl triflate (0.75 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.00 mmol) in DMF (1.0 mL) containing 2 mol % (ca. 5 mg) of $Ni(dppe)Cl_2$ as a catalyst produced a 61% isolated yield of pure triphenylphosphine. These conditions compare most favorably with related triflate−diarylphosphine couplings reported in the literature where long reaction times and higher equivalents of the base and the Ni catalyst were required.[3]

In conclusion, we have shown that rapid, direct transition metal-catalyzed C−P(III) bond formations can be achieved by microwave dielectric heating, employing a variety of homogeneous and heterogeneous catalytic systems. We believe that the observed rate enhancements are due to the rapid "in core" heating of the reaction mixture due to significantly higher temperatures of microwave energy and are not a consequence of a specific ("nonthermal") microwave effect.[13] Further work in order to improve the transition metal catalysts and to achieve higher product yields is in progress. The application of this high-speed methodology to access synthetically valuable triarylphosphine ligands in a combinatorial fashion,[14] involving a broad range of aryl halide/triflate and secondary phosphine building blocks, is currently under investigation.

Acknowledgment. We thank Personal Chemistry AB (Uppsala, Sweden) for the use of the Smith Synthesizer.

Supporting Information Available: Full experimental details for all transformations described. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] **CAUTION!** Extreme care must be taken in order to avoid arcing (see ref 10) and destruction of the glass vessel in exposing these metal-doped vials (Figure S1 in Supporting Information) to microwave irradiation. For the use of Pd-doped porous glass tubing in microwave-assisted C−C coupling reactions, see the following: Li, J.; Mau, A. W.-H.; Strauss, C. R. *Chem. Commun.* **1997**, 1275−1276.

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[13] For a discussion of specific microwave effects, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (b) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863−1866

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