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Microwave-Assisted Synthesis of Phenylene-Bridged Aminophosphine Ligands: Acceleration of N-Arylation and Aryl Fluoride Phosphorylation Reactions

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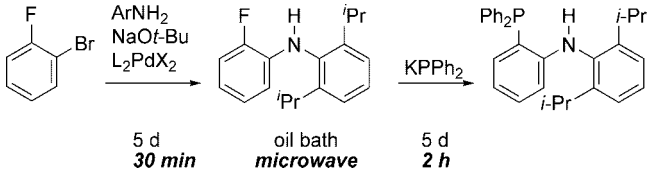
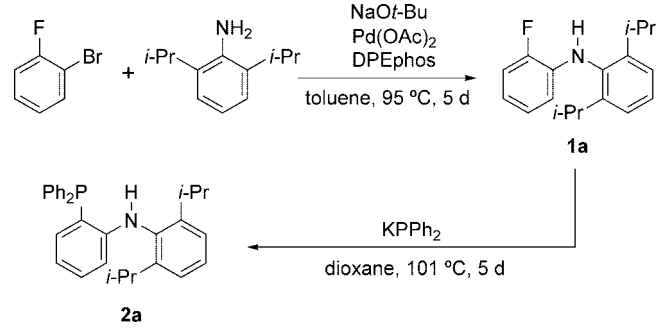


Hindered β-aminoarylphosphines show promise as bidentate ligands for metal centers, but their reported synthesis requires heating at high temperatures for several days. Herein are reported conditions by which the two steps composing this synthesis, Buchwald−Hartwig amination and nucleophilic phosphorylation reactions, may both be completed in less than 3 h using microwave irradiation. The effects of several parameters on the outcome of the amination reaction are discussed, as are some indications of the scope within which each of these microwave protocols is effective.

Chelating aminophosphine ligands have long been used to support many main group, rare earth, and transition metal complexes.[1,2] They boast, among other advantages, an ability to bind as either neutral or anionic donors or to iterate between these states in catalytic systems.[3–6] One of the simplest such ligands, 2-diphenylphosphinoaniline, has been used regularly for decades, and its N-alkylated and N-silylated derivatives are easily accessed by simple substitution chemistry. In contrast, aryl-substituted analogues were reported only recently, after advances in C−N coupling methodology made their synthesis a straightforward undertaking.[7–10,11,12] Since Liang and co-workers first reported the preparation of these ligands in 2003, they have been used to prepare a variety of complexes including fluorescent copper species,[13] low valent aluminum[14] and zinc[11] centers, and nickel complexes modeling olefin oligomerization catalysts.[15,16]

SCHEME 1. Reported Synthesis of Aminophosphine Ligand[11]



If anything has limited the use of these promising bidentate ligands, it has been the time required for their preparation. Liang's two-step synthesis proceeds via the palladium-catalyzed coupling of an aniline to *o*-bromofluorobenzene, followed by nucleophilic phosphorylation at the fluoride substituent of the resulting diarylamine **1** (Scheme 1).[11] While each of these reactions proceeds in excellent yield, preparation of the bulkier reported ligand **2a** requires a total of 10 days heating at temperatures at and above 95 °C. A faster reaction could conserve time and energy and significantly increase the convenience with which researchers may explore these ligands' potential.

We have sought to increase the practical accessibility of aryl-substituted aminophosphine ligands by using microwave irradiation to expedite their syntheses. In the last 20 years, laboratory microwaves have been found to accelerate many reactions,[17–20] including Buchwald−Hartwig coupling reactions, similar to the first step of Liang's synthesis.[21–28] The phospho-

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TABLE 1. Temperature, Time, and Solvent Dependence of N-Arylation Microwave Reactions[a]

entry	temp (°C)	time (min)	solvent	yield[b] (%)
1	100	15	THF	69 (54)
2	100	30	THF	95 (89)
3	80*c*	15	toluene	38
4	100	15	DMF	60
5	100	15	(neat)	33−55
6	120	15	THF	65
7	120	30	THF	66
8	80	15	THF	48

[a] Reagents and typical conditions: 1.42 mmol 2,6-diisopropylaniline, 1.45 mmol *o*-bromofluorobenzene, 1.71 mmol NaO*t*-Bu, 0.0071 mmol $Pd(OAc)_2$, 0.0078 mmol DPEphos, 4 mL of solvent. [b] Yields are based on quantities of product relative to starting materials and side products quantified by gas chromatography. Where applicable, isolated yields are given in parentheses. [c] This was the highest temperature achieved by this sample.

TABLE 2. Palladium Source and Ligand Dependence of N-Arylation Microwave Reactions[a]

entry	Pd source	ligand[b] (equiv)	yield[c] (%)
1	$Pd(OAc)_2$	DPEphos (1.1)	95 (89)
2	$PdCl_2$	DPEphos (1.1)	94
3	$Pd(dba)_2$[d]	DPEphos (1.1)	46
4	$Pd(OAc)_2$	BINAP (1.1)	93
5	$Pd(OAc)_2$	DPPF (1.1)	96
6	$Pd(OAc)_2$	DPPE (1.1)	45
7	$Pd(OAc)_2$	PPh_3 (2.2)	21
8	$Pd(OAc)_2$	DPEphos (1.5)	97
9	$Pd(OAc)_2$	DPEphos (0.5)	43
10[e]	$Pd(OAc)_2$	DPEphos (1.1)	90 (84)

[a] Reagents and typical conditions: 1.51 mmol 2,6-diisopropylaniline, 1.52 mmol *o*-bromofluorobenzene, 1.75 mmol NaO*t*-Bu, 0.0072 mmol $Pd(OAc)_2$, 0.0090 mmol DPEphos, 4 mL of THF, 30 min heating at 100 °C. [b] DPEphos = bis(2-phenylphosphinophenyl)ether, BINAP = bis-2, 2′-bis(diphenylphosphino)-1,1′-binapthyl, DPPF = bis(1,1′-diphenylphosphino)ferrocene, DPPE = 1,2-bis(diphenylphosphino)ethane. [c] Yields are based on quantites of starting material, product, and unidentified side products observed by gas chromatography. Where applicable, isolated yields are given in parentheses. [d] dba = dibenzylideneacetone. [e] Reaction prepared on bench and flushed with nitrogen prior to heating.

rylation reaction is also a good candidate for such acceleration, as it involves polar reagents inherently suited to absorbing microwaves.[18,20] The most relevant reported conditions for microwave-accelerated N-arylation[22,25] proved ineffective in coupling the sterically demanding substrates of interest, and we are aware of no prior reports of microwave-accelerated aryl fluoride phosphorylation, so we have developed conditions under which both couplings occur efficiently. Herein we describe microwave-assisted procedures by which these ligands may be prepared in high yields in less than 3 h total reaction time.

N-Arylation. Literature reports describe microwave conditions for the coupling of 4-aminobenzophenone with 2,4-difluorobromobenzene[25] and for the amination of *p*-bromotoluene with aniline.[22] Neither set of conditions achieved favorable results using the more sterically demanding 2,6-diisopropylaniline substrate. New conditions for its coupling with *o*-bromofluorobenzene were evaluated by screening conditions on a small scale (ca. 0.25 g of *o*-bromofluorobenzene) and assessing reaction outcomes by gas chromatography; most of these reactions were intentionally run to less than full conversion in order to best identify differences in yields among the various conditions, and the key results are summarized in Tables 1–3.

Temperature, time, and solvent conditions were screened using the same palladium source and ligand employed in the conventional synthesis of the target compound **1a** (Table 1). Interestingly, conditions nearly identical to those reported for the much slower oil-bath reaction could be used to effect >95% conversion in 30 min under microwave conditions, the only differences being a temperature increase of 5 °C and the substitution of THF for toluene as solvent (entry 2). (We have not rigorously mapped the differences between microwave and oil-bath conditions in this system, but subjection of an identical reaction mixture to conventional heating at 100 °C for 1 h yielded a reaction mixture still dominated by starting materials.) Although THF is generally considered to be a solvent only marginally polar enough for effective microwave heating,[18,20] the desired reaction temperature was typically achieved within 1 min at a maximum power of 1600 W. (After the initial heating, the reaction temperature was usually maintained at powers of approximately 500 W.) This efficiency may be a consequence of the relatively high concentration of more polar substrates in the reaction mixture (ca. 0.2 M each in aniline, haloarene, and base), which likely absorb much of the incident microwave radiation. However, the target temperature was not achieved in a timely manner when benzene or toluene was used as the solvent, and at comparable reaction times, syntheses in these solvents yielded incomplete conversion (entry 3). DMF (entry 4) offered no obvious advantage relative to THF and gave a greater proportion of unidentified side products than did other solvents, which showed incomplete conversion of starting materials rather than unwanted side products. Although the best results were achieved at very high substrate concentrations, solvent-free conditions yielded inconsistent and generally poor results (entry 5). Higher reaction temperatures resulted in incomplete conversion even at *longer* reaction times, suggesting catalyst deactivation occurred. This sensitivity to higher temperatures offers one possible explanation for the considerable acceleration achieved by microwave irradiation in this system: this method may avoid catalyst decomposition that would occur under less homogeneous heating conditions, maintaining the effective loading closer to the 0.5 mol % originally added.

Palladium acetate and palladium chloride showed very similar activities, while $Pd(dba)_2$ gave poorer yields (Table 2). The chelating phosphine ligands BINAP, DPPF, and DPEphos all gave relatively similar yields (entries 4−6), and even DPPE and PPh_3 gave significant, although dramatically lower, yields of product (entries 6 and 7). This stands in marked contrast to Skjaerbaek's work, which identified DPE and DPPF as particularly *ineffective* ligands in microwave-assisted N-arylation of electron-poor anilines.[25] Yields increased with ligand loading up to a maximum L:Pd ratio of 1.5:1, although little advantage was observed beyond 1 equiv of ligand relative to palladium. Reactions were typically conducted under air-free conditions; abandonment of these precautions led to marked drops in yield, although sparging the reaction mixture with nitrogen prior to heating produced results roughly comparable to those achieved

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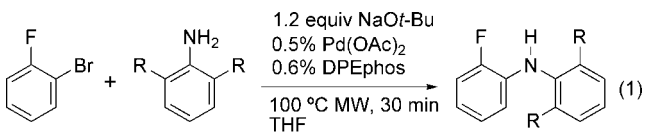
TABLE 3. Stoichiometry of N-Arylation Microwave Reactions[a]

entry	2,6-diisopropylaniline (mmol)	*o*-bromofluoro-benzene (mmol)	NaO*t*-Bu (mmol)	yield[b] (%)
1	1.42	1.45	1.71	69 (54)
2	1.40	3.21	1.70	71
3	3.15	1.41	1.74	65
4	1.35	1.39	2.67	70

[a] Reagents and typical conditions: 0.0071 mmol $Pd(OAc)_2$, 0.0078 mmol DPEphos, 4 mL of THF, 15 min at 100 °C. [b] Yields are based on quantities of product relative to starting materials and side products quantified by gas chromatography. Where applicable, isolated yields are given in parentheses.

using distilled THF and mixing reagents in an inert atmosphere glovebox (entry 10).

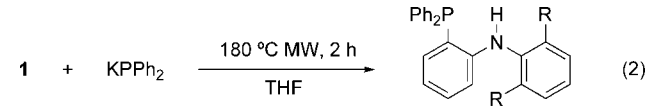
Although some reports of microwave-accelerated Buchwald–Hartwig coupling suggest there to be benefits of using a significant excess of aniline or base,[22] this was found not to be advantageous in this system (Table 3). Indeed, yields were equally as high when equimolar quantities of the two coupling partners and a slight excess of base were used but did not drop appreciably when any of these reagents were added in significant excess.



1a R = *i*-Pr (90%)
1b R = CH_3 (85%)

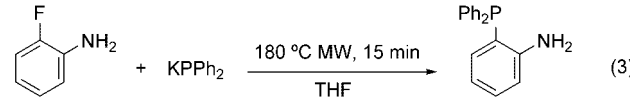
While the optimum conditions summarized in eq 1 proved quite effective for bulky anilines, it shows surprisingly poor generality. While these conditions successfully converted 2,6-dimethylaniline into *N*-(2-fluorophenyl)-2,6-dimethylaniline (**1b**) in 85% yield, application of the same procedures to the coupling of *p*-toluidine with *o*-bromofluorobenzene resulted in poor yields on the order of 10–20%, which could be improved only by much higher catalyst loadings. This suggests that the conditions identified above may not merely tolerate bulky aryl substituents but may actually depend on them for success; optimization of conditions for smaller substrates was not explored, as previous reports[22] already detail microwave conditions suitable for preparing smaller fluoroanilines.

Phosphorylation. Phosphorylation conditions for the resulting *o*-fluoroanilines **1** were developed by evaluating reaction yields by ^{31}P and ^{19}F NMR spectroscopies prior to workup. In all reactions, an *o*-fluoroaniline was added to commercially supplied 0.50 M $KPPh_2$ in THF, and the resulting dark red solutions were microwaved without additional solvent (eq 2). The bulkier starting material **1a** reacted at 120 °C, and although all starting $KPPh_2$ was consumed within 3 h, several unidentified byproducts were identified by ^{31}P NMR at the end of this time, and some of the aryl fluoride **1a** remained—isolated yields were correspondingly low. Use of additional $KPPh_2$ conferred no obvious advantage under these conditions. These results were modestly improved at 150 °C, and substantially improved at 180 °C, where 120 min irradiation resulted in complete consumption of $KPPh_2$ and fluoroaniline **1a**. The ^1H NMR spectrum of the reaction mixture confirmed the presence of the expected reaction product, and ligand **2a** was isolated in 82% as a pure white solid. The same conditions also afforded **2b** from **1b** in 87% isolated yield.



2a R = *i*-Pr (82%)
2b R = CH_3 (87%)

The investigation of phosphorylation conditions was also extended to include the preparation of the parent ligand, primary aniline *o*-diphenylphosphinoaniline (**2c**), the synthesis of which has historically been a cumbersome process.[8] Catalytic approaches to its preparation have recently been described,[29,30] and the traditional thermal phosphorylation of 2-fluoroaniline by $KPPh_2$ was recently reported to proceed in 55% yield after 4 days reflux in DME.[31] Using the microwave, the same reaction runs to quantitative spectroscopic yield in 15 min at 180 °C, and the white, crystalline product **2c** was isolated in 79% yield (eq 3). This result suggests that, in contrast to the amination reaction described above, the benefits of this microwave technique should extend broadly to related phosphorylation reactions.



2c (79%)

These procedures offer a convenient and efficient route by which to prepare aryl-substituted and unsubstituted aminoarylphosphine ligands from inexpensive starting materials in a matter of hours, marking an acceleration of 2 orders of magnitude relative to the methods previously described in the literature. The use of microwave conditions greatly accelerates both the palladium-catalyzed C–N coupling and phosphide substitution reactions composing the syntheses of interest, without otherwise requiring dramatic changes to the reagents or stoichiometry originally reported. The similarity of these conditions suggests that the advantages of microwave irradiation in the amination reaction may best be credited to improved catalyst longevity, and the phosphorylation reaction employs microwave irradiation simply as an efficient means by which to reach and maintain an elevated reaction temperature.

Experimental Section

Microwave Heating. A 1600 W CEM MARS multimode microwave was used for all heating, which was conducted at constant temperature monitored by a fiber optic RTP-300 Plus probe. Initial ramping times of roughly 1–2 min were typically observed. Reactions were conducted in CEM GreenChem Plus glass vessels, which were loaded under nitrogen atmosphere using dried, deoxygenated solvents and reagents.

***N*-(2-Fluorophenyl)-2,6-diisopropylaniline (1a).** A microwave vessel was charged with 2,6-diisopropylaniline (5.15 g, 29.1 mmol), *o*-bromofluorobenzene (5.10 g, 29.1 mmol), NaO*t*-Bu (3.35 g, 34.9 mmol), $Pd(OAc)_2$ (0.033 g, 0.145 mmol), and DPEphos (bis(2-phenylphosphinophenyl)ether) (0.094 g, 0.174 mmol) and suspended in THF (15 mL) under nitrogen. The vessel was closed and heated to 100 °C by microwave (ca. 500 W after the initial ramp) for 30 min with stirring. The resulting reaction mixture was

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washed with 30 mL of H_2O, and the organic fraction was evaporated to dryness. The resulting dark oil was extracted with pentane (100 mL) and filtered through a small plug of silica gel, and volatiles were removed in vacuo to yield yellow-orange oil **1a** (7.10 g, 90%). The compound was identified by ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectroscopies.[11]

***N*-(2-Fluorophenyl)-2,6-dimethylaniline (1b).** The same method and molar ratios described for **1a** afforded **1b**[14] from 2-6-dimethylaniline as pale yellow flaky crystals (2.15 g, 85%).

***N*-(2-Diphenylphosphinophenyl)-2,6-diisopropylaniline (2a).** A microwave vessel was charged with **1a** (1.34 g, 4.94 mmol) and $KPPh_2$ (0.50 M in THF, 11 mL, 5.5 mmol) under nitrogen. **Caution:** No stir bar was used, as the Teflon coating was found to degrade significantly under the reaction conditions. The vessel was closed and heated to 180 °C by microwave for 120 min (ca. 800 W after the initial temperature ramping). Volatiles were removed in vacuo, and the reaction was quenched with deoxygenated water (10 mL). Organics were extracted with deoxygenated CH_2Cl_2 (2 × 10 mL), and the extract was filtered through a plug of silica. Volatiles were removed from the filtrate in vacuo to yield a yellow solid that was washed with boiling methanol to yield off-white powder **2a** (1.76 g, 82%). Mp 97−99 °C. The compound was identified by ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopies.[11]

***N*-(2-Diphenylphosphinophenyl)-2,6-dimethylaniline (2b).** The same method and molar ratios described for **2a** afforded **2b**[14] from **1b** as a white crystalline solid (1.65 g, 87%).

2-Diphenylphosphinoaniline (2c). A microwave vessel was charged with *o*-fluoroaniline (1.11 g, 10.0 mmol) and $KPPh_2$ (0.50 M in THF, 20.0 mL, 10.0 mmol) under nitrogen. The vessel was closed and heated by microwave to 180 °C for 15 min (ca. 800 W after the initial temperature ramping). The reaction mixture was quenched with deionized water (15 mL), and the organics were extracted into benzene (2 × 20 mL). The extract was filtered through a short alumina plug and recrystallized from boiling EtOH to yield **2c** as a white powder (2.18 g, 79%). Mp 81−82 °C, lit[8] 82−83 °C.[32]

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Supporting Information Available: General experimental procedures, selected details of synthesis and characterization, and ^1H NMR spectra of the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) NMR data for this well-known compound are included in the Supporting Information.