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Nickel-Catalyzed Cross-Coupling of Phenols and Arylboronic Acids Through an In Situ Phenol Activation Mediated by PyBroP

Guo-Jun Chen, Jie Huang, Lian-Xun Gao, and Fu-She Han*[a]

Abstract: A new method for the Suzuki–Miyaura cross-coupling of phenols and arylboronic acids through in situ phenol activation mediated by PyBroP is presented. The reaction proceeds efficiently by using cost-effective, markedly stable [$NiCl_2$(dppp)] (dppp = 1,3-bis(diphenylphosphino)propane) as the catalyst in only 5 mol% loading, as well as in the absence of extra ligands. The method exhibits broad applicability and high efficiency towards a wide range of both phenols and boronic acids, including activated, nonactivated, deactivated, and heteroaromatic coupling partners. In addition, various functional groups, such as ether, amino, cyano, ester, and ketone groups, are compatible with this transformation. Notably, arylboronic acids containing an unprotected NH_2 group and 2-heterocyclic boronic acids, which are generally problematic for coupling under conventional conditions, are also viable substrates, although moderate yields were obtained for sterically hindered substrates. Consequently, the in situ cross-coupling methodology coupled with the use of an inexpensive and stable nickel catalyst provides a rapid and efficient pathway for the assembly of biaryls and heterobiaryls with structural diversity from readily available phenol compounds.

Keywords: biaryls · cross-coupling · homogeneous catalysis · nickel · phenols · phosphonium salts

Introduction

The construction of biaryl and heterobiaryl compounds has attracted considerable interest because these structural motifs are core scaffolds that are found in a myriad of polymers, bioactive compounds, supramolecular structures, and so forth.[1] Numerous reports have demonstrated that in recently developed approaches, the transition-metal-catalyzed cross-coupling is an exceedingly powerful transformation in which phenol compounds are the most widely available and inexpensive starting material for biaryl assembly. However, several limitations of the catalyst systems, such as poor thermal stability, high cost, and sensitivity towards both air and moisture, strongly restrict their general applicability in industrial processes.[2] Moreover, most of the traditional methods require prior activation of inert phenols to a more reactive, but less stable, precursor. These activation strategies include the formation of aryl triflates,[3] sulfonates,[4] ethers,[5] esters,[6] carbamates,[7] carbonates,[7a] sulfamates,[7a] and phosphoramides.[8] Undoubtedly, such a stepwise process is not only time-consuming and economically less effective, but also generates more waste.

Very recently, the in situ activation of phenols through the formation of inorganic salts (e.g., ArOMgX)[9] and organic phenolic phosphonium salts,[10,11] or pivalate esters[6a] has emerged as an attractive approach for C–C bond formation. These novel strategies provide an important advantage over the traditional ones; they merge the phenol activation and subsequent cross-coupling into a single operation and, therefore, make the transformation more practical in terms of efficiency, economy, and environmental impact.[10b,d] However, the generality of inorganic salt protocols remains to be determined because the use of strongly basic, as well as nucleophilic, MeMgBr as the activating agent would be problematic for substrates containing labile functional groups, such as ester and ketone groups. Although the phosphonium salts have been extensively studied by Kang et al. and other groups,[10,11] the pathways have limited scope and utility because they usually necessitate the use of α-N-activated tautomerizable N-heterocycles (cyclic amides, Scheme 1, top) as substrates. Moreover, successful coupling requires a high loading of expensive Pd catalysts (typically 5 mol%). Consequently, a practical solution for the effective coupling of common phenols (Scheme 1, bottom) through in situ activation has been less developed, although such transformation is expected to be feasible.[11]

We have paid particular attention to this issue and initiated a study towards the development of a highly active and practical catalyst system. Our efforts have been focused on inexpensive and readily available Ni-based catalysts because we have demonstrated previously that an appropriate combination of $NiCl_2$ and 1,3-bis(diphenylphosphino)propane (dppp) is a highly active precatalyst for the coupling of aryl phosphoramides.[4h,8] Herein, we disclose that [$NiCl_2$(dppp)]

[a] Dr. G.-J. Chen,[+] J. Huang,[+] Prof. L.-X. Gao, Prof. Dr. F.-S. Han
Changchun Institute of Applied Chemistry
Chinese Academy of Sciences
5625 Renmin Street, Changchun, Jilin 130022 (P.R. China)
E-mail: fshan@ciac.jl.cn

[+] These authors contributed equally to this work.

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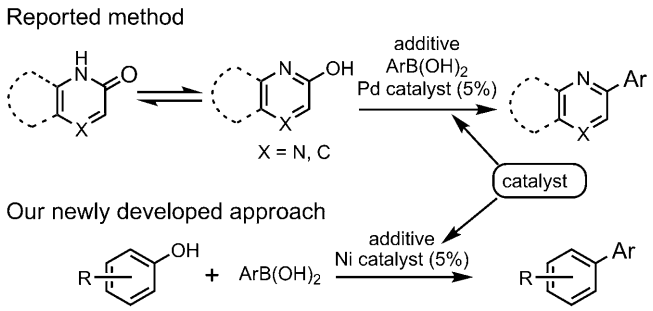


Scheme 1. Reported versus newly developed methods for in situ activation and cross-coupling of Ar-OHs.

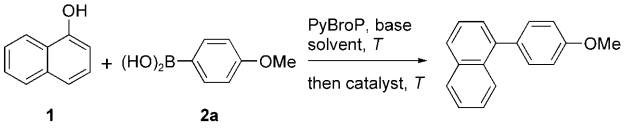
is a highly active, inexpensive, and markedly stable catalyst that allows effective cross-coupling of common phenols through the in situ activation approach.

Results and Discussion

At the outset of this study, we investigated the cross-coupling of phenols with arylboronic acids (Suzuki–Miyaura coupling) since this transformation has been recognized as the most important method[12] for the diverse construction of biaryls owing to the numerous advantages that pertain to the use of boronic acids, such as wide availability, low toxicity, and stability to heat, air, and moisture, as well as the ease of removal of boron-containing by-products.[6a,13] Accordingly, optimization of the reaction conditions was carried out by employing the reaction of 1-naphthol (**1**) with 4-methoxyphenylboronic acid (**2a**) as a model system (Table 1). In comparison with the traditional stepwise processes, the screening of suitable conditions for the one-pot transformation is far more challenging since it requires an appropriate combination of an activating agent and a catalyst that can not only activate phenols efficiently, but also holds high catalytic activity in the following catalytic cycle.

Thus, various activating systems were examined first, including PPh_3/I_2, PPh_3/NCS, PPh_3/NBS, PPh_3/NIS, $P(OMe)_3$/NBS, and $P(OMe)_3/I_2$ (NCS = *N*-chlorosuccinimide; NBS = *N*-bromosuccinimide; NIS = *N*-iodosuccinimide). The results showed that although these systems could react with phenols to form phenolic phosphonium salts $[(ArOPR_3)^+X^-]$, the subsequent metal-catalyzed cross-coupling with boronic acid was unsuccessful in the presence of various Pd or Ni catalysts. Further exploration eventually revealed that bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), which has been shown to be a mild and effective agent for the in situ activation of α-N-activated heterocyclic arenols,[10,11] was also a suitable agent for the activation of common phenols. However, here, a combination of Et_3N and K_3PO_4 (or K_2CO_3) as the base coupled with an elevated reaction temperature (80–100 °C) is crucial for effective activation of phenols. The absence of either the organic or the inorganic base resulted in an incomplete or slow conversion of phenols to the corresponding phosphonium salts.[14] This

Table 1. Optimization of cross-coupling conditions.[a]



1 2a

	Catalyst [mol %]	Ligand	PyBroP [equiv]	Yield [%][b]
1	$[PdCl_2(dppf)]$ (5)	PCy_3	1.5	4
2	$[PdCl_2(dppf)]$ (5)	PCy_3	1.5	7[c]
3	$[PdCl_2(cod)]$ (5)	PCy_3	1.5	n.r.[d]
4	$[PdCl_2(cod)]$ (5)	dppe	1.5	16
5	$[PdCl_2(cod)]$ (5)	dppb	1.5	15
6	$[PdCl_2(cod)]$ (5)	dppp	1.5	13
7	$[NiCl_2(PCy_3)_2]$ (5)	PCy_3	1.5	39
8	$[NiCl_2(PCy_3)_2]$ (5)	PCy_3	1.5	22[e]
9	$[NiCl_2(PCy_3)_2]$ (5)	dppe	1.5	4
10	$[NiCl_2(PCy_3)_2]$ (5)	dppb	1.5	2
11	$[NiCl_2(PCy_3)_2]$ (5)	dppp	1.5	27
12	$NiCl_2$ (5)	dppp	1.5	46
13	$[NiCl_2(dppp)]$ (5)	–	1.5	70[f]
14	$[NiCl_2(dppp)]$ (5)	–	1.5	81[f,g]
15	$[NiCl_2(dppp)]$ (5)	–	1.5	66[f,g,h]
16	$[NiCl_2(dppp)]$ (5)	–	1.0	41[f,g]
17	$[NiCl_2(dppp)]$ (5)	–	1.2	43[f,g]
18	$[NiCl_2(dppp)]$ (2)	–	1.5	52[f,g]
19	$[NiCl_2(dppp)]$ (3)	–	1.5	59[f,g]

[a] Reaction conditions: 1-naphthol (**1**; 0.5 mmol), PyBroP, Et_3N (3.0 equiv), K_3PO_4 (3.0 equiv) in dioxane (3 mL) at 100 °C for 3 h; then catalyst, ligand (10 mol %), and 4-methoxyphenylboronic acid **2a** (1.0 mmol) at 100 °C; dppf = 1,1′-bis(diphenylphosphino)ferrocene; Cy = cyclohexyl; cod = 1,5-cyclooctadiene; dppe = 1,2-bis(diphenylphosphino)-ethane; dppb = 1,4-bis(diphenylphosphino)butane. [b] Isolated yield. [c] 5 % (v/v) water was added to the solvent. [d] No reaction. [e] K_2CO_3 was used as the base. [f] No extra ligand was added. [g] K_3PO_4 (4.0 equiv) was used. [h] The reaction was performed by adding all the reagents and the catalyst simultaneously.

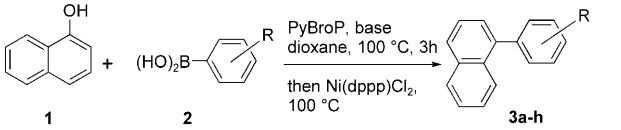
is possibly due to the poor solubility of inorganic bases in the dioxane solvent, and the volatile nature of organic Et_3N at the reaction temperature employed (vide supra). Ultimately, separate use of either an inorganic or organic base decreases the efficiency of the reaction between phenols and PyBroP.

By using PyBroP as the in situ activation agent, the screening of a catalyst system for the subsequent cross-coupling showed that the use of several Pd-based catalysts, such as $[PdCl_2(dppf)]$ and $[PdCl_2(cod)]$, led to inefficient coupling either in the absence or presence of phosphine ligands, such as PCy_3, dppe, dppp, dppb, and dppf (Table 1, entries 1–6). In contrast, the Ni-based catalysts were shown to be far more active than the Pd catalysts, as shown by a comparison of the results in Table 1, entry 7 with those in Table 1, entries 1 and 3. Thus, after careful evaluation of various reaction parameters, including the effect of Ni-based catalysts, ligands, bases, the molar equivalent of PyBroP, and temperature (Table 1, entries 8–19), we were pleased to find that the $[NiCl_2(dppp)]$ complex[15] was a competent catalyst that could affect the cross-coupling of 1-naphthol with 4-methoxyphenylboronic acid in 81 % yield, even in the absence of extra supporting ligands (Table 1, entry 14). However, if the reaction was carried out under otherwise identical parame-

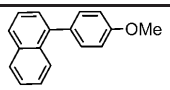
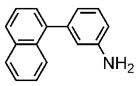
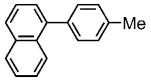
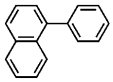
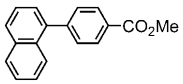
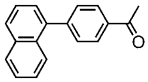
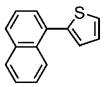
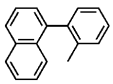
ters to those in Table 1, entry 14, but by adding the reagents and catalyst simultaneously, a somewhat decreased yield (66%) was observed (Table 1, entry 15). In addition, reducing the molar ratio of PyBroP or the catalyst loading led to a significantly decreased yield (Table 1, entries 16–19). Thus, the optimized reaction conditions for the one-pot Suzuki–Miyaura coupling of common phenols are PyBroP (1.5 equiv), K_3PO_4 (4.0 equiv), Et_3N (3.0 equiv), 100°C, 3 h in dioxane (3 mL)[16] followed by addition of boronic acid (2.0 equiv) and [$NiCl_2$(dppp)] (5 mol%).

With the optimized reaction conditions available, we then examined the generality of this protocol. First, the feasibility of the method was evaluated by performing the coupling of 1-naphthol with a wide range of arylboronic acids (Table 2). The results show that 1-naphthol couples smoothly with various boronic acids that are substituted by electron-donating (Table 2, entries 1 and 2), -neutral (Table 2, entries 3 and 4), or -withdrawing groups (Table 2, entries 5 and 6) on the ring periphery of the boronic acid. Good to excellent yields were observed for all of the boronic acids with different electronic natures. In addition, a heteroaromatic boronic acid (2-thienylboronic acid) also serves as a viable substrate, providing the heterobiaryl compound in 60% yield (Table 2, entry 7). Finally, the transformation was shown to be somewhat less efficient for a sterically hindered boronic acid (Table 2, entry 8).

Table 2. Cross-coupling of 1-naphthol (**1**) and various arylboronic acids (**2a–h**) under the optimized reaction conditions.[a]



1 2 3a-h

	$ArB(OH)_2$	Ar–Ar′	Yield [%][b]
1	**2a**, R = 4-OMe		81
2	**2b**, R = 3-NH_2		74
3	**2c**, R = 4-Me		84[c]
4	**2d**, R = H		70[c]
5	**2e**, R = 4-CO_2Me		92
6	**2f**, R = 4-C(O)Me		71
7	**2g**, R = 2-thienyl		60
8	**2h**, R = 2-Me		50[c]

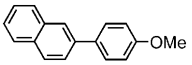
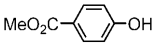
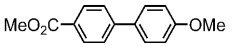
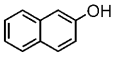
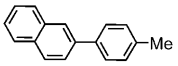
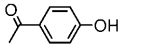
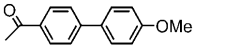
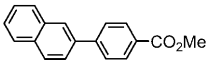
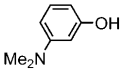
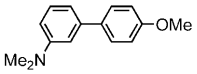
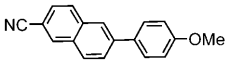
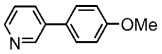
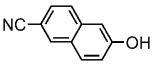
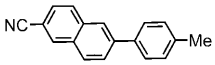
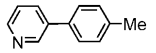
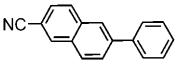
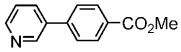
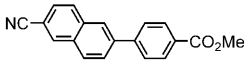
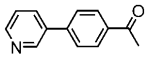
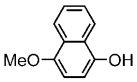
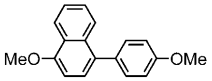
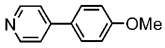
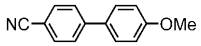
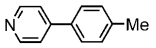
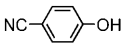
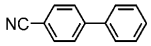
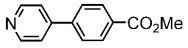
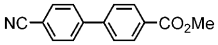
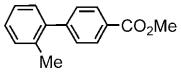
[a] Reaction conditions: 1-Naphthol (**1**; 0.5 mmol), PyBroP (1.5 equiv), Et_3N (3.0 equiv), K_3PO_4 (4.0 equiv) in dioxane (3 mL) at 100°C for 3 h; then [$NiCl_2$(dppp)] (5 mol%) and arylboronic acid **2** (1.0 mmol) at 100–110°C, 4–24 h. [b] Isolated yield. [c] Yield was determined by ^{1}H NMR analysis due to contamination by a small amount of an inseparable by-product derived from homocoupling of boronic acid.

Here, two transformations are particularly worth noting. First, the coupling of a boronic acid containing a free NH_2 group (Table 2, entry 2) occurred exclusively at the boronic acid position, with the unprotected NH_2 functional group remaining intact. In contrast, conventional coupling with palladium catalysts generally requires prior protection of amino groups.[17] Thus, the in situ activation of phenol, along with the direct use of unprotected amino boronic acids, provides a much more straightforward pathway for the construction of polyaromatic-ring-containing amines. Compounds of this class are core motifs in or important building blocks for the construction of a broad range of useful targets, such as pharmaceuticals, functional materials, coordination compounds, and ligands through, for instance, the well-established Buchwald-Hartwig coupling reactions[18] (i.e., C–N bond formation reactions). Second, the ability to couple with unstable 2-thienylboronic acid by use of the nickel catalyst (Table 2, entry 7) is also attractive as effective coupling of 2-heterocyclic boronic acids is usually problematic and suffers from rapid deboronation under typical conditions,[19] although a generally applicable and highly efficient catalyst system based on palladium has been developed very recently by Buchwald and co-workers.[19]

Next, the reaction efficiency of the synthetic process was further inspected by varying the phenol components. As shown in Table 3, 2-naphthol underwent smooth coupling with electron-rich, -neutral, and -deficient boronic acids (Table 3, entries 1–3). Moreover, naphthol analogues containing either a strongly electron-withdrawing CN or a strongly electron-donating OMe group could be converted to the desired biaryls in good to excellent yields (Table 3, entries 4–8). Most interestingly, we have also observed that this transformation is tolerant of various non-fused (i.e., less electron-deficient) phenol compounds. For instance, several phenol compounds substituted by an electron-withdrawing CN, CO_2Me, or C(O)Me functional group could be transformed smoothly into the corresponding cross-coupled products in high yields (Table 3, entries 9–13). In addition, effective coupling was observed for a phenol containing a strongly electron-donating NMe_2 substituent (Table 3, entry 14). Finally, heteroaromatic phenols, such as 3- and 4-hydroxylpyridines, are superb substrates, delivering heterobiaryls in excellent yields (Table 3, entries 15–21). It should be mentioned that the cross-coupling of the *ortho*-substituted phenol was somewhat challenging, providing the desired products in 39% yield (Table 3, entry 22).

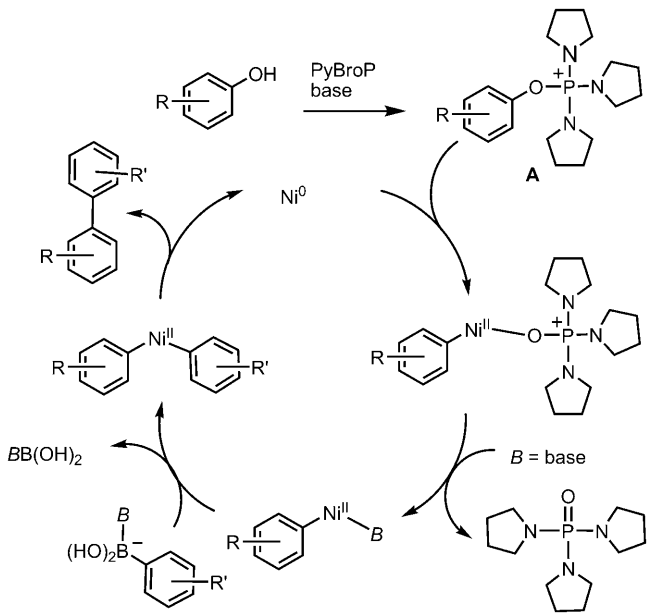
For a plausible mechanism for this transformation, we have confirmed through the experiments that in the first stage, the phenol and PyBroP form a phosphonium salt (**A**;[14] Scheme 2). This species may act as an activated phenolic intermediate for the subsequent cross-coupling reaction. Concerning the Ni^0-catalyzed coupling reaction, al-

Table 3. Cross-coupling of various phenols and arylboronic acids under the optimized reaction conditions.[a]

	Ar–OH	$ArB(OH)_2$	Product	Yield [%][b]		Ar–OH	$ArB(OH)_2$	Product	Yield [%][b]
1		**2a**		78	12		**2a**		70
2		**2c**		80[c]	13		**2a**		75
3		**2e**		72	14		**2a**		62, 73[d]
4		**2a**		81	15		**2a**		80
5		**2c**		97	16		**2c**		94
6		**2d**		77	17		**2e**		74
7		**2e**		95	18		**2f**		82
8		**2a**		78	19		**2a**		85[e]
9		**2a**		82	20		**2c**		90[e]
10		**2d**		79	21		**2e**		93[e]
11		**2e**		89	22		**2e**		39

[a] Reaction conditions: phenol (0.5 mmol), PyBroP (1.5 equiv), Et_3N (3.0 equiv), K_3PO_4 (4.0 equiv) in dioxane (3 mL) at 100 °C for 3 h; then [$NiCl_2$(dppp)] (5 mol %) and arylboronic acid **2** (1.0 mmol) at 100–110 °C, 4–24 h. [b] Isolated yield. [c] Yield was determined by ^1H NMR analysis due to contamination by a small amount of inseparable by-product derived from homocoupling of boronic acid. [d] catalyst (10 mol %) was used. [e] DMF (10 % (v/v)) was used as a co-solvent.

though the detailed catalytic cycle is not clear at present, the mechanism may be similar to that proposed for the palladium-catalyzed cross-coupling of α-N-activated heterocycles mediated by PyBroP, involving sequential oxidative addition of Ni^0 to **A**, transmetalation, and reductive elimination.[10,11] Such a cycle is essentially similar to the general Pd- or Ni-catalyzed cross-coupling mechanism for aryl halides (pseudo-halides) and boronic acids, as originally suggested by Suzuki[20] and Percec.[21]



Scheme 2. A proposed mechanism for the [$NiCl_2$(dppp)]-catalyzed in situ cross-coupling of phenols with arylboronic acid mediated by PyBroP.

Conclusion

We have achieved successfully the Suzuki–Miyaura cross-coupling of phenols through in situ phenol activation mediated by PyBroP. More significantly, the reaction proceeds smoothly by using the cost-effective, highly stable [$NiCl_2$(dppp)] catalyst in only 5 mol % loading, as well as in the absence of extra supporting ligands. In addition, the method not only exhibits broad applicability and high efficiency towards both a wide variety of phenols and boronic acids, including activated, non-activated, deactivated, and heteroaromatic substrates, but also is tolerant of various functional groups on the aromatic rings, such as OMe, NH_2, CN, CO_2Me, and C(O)Me groups. Thus, this method offers several advantages over the available in situ activation strategies in terms of the cost and efficiency of the catalyst, as

well as the scope of the substrates. As a result, the method provides a rapid and efficient pathway for the diverse construction of biaryls and heterobiaryls from readily available and cheap phenols. Finally, to best use this discovery, we are currently carrying out other metal-catalyzed C–X (X = C, N, etc.) bond formation reactions through the in situ activation of phenols.

Experimental Section

General methods: All reactions were carried out under a N_2 atmosphere. The dioxane solvent was dried over molecular sieves (4 Å). Anhydrous $NiCl_2$ and dppp, dppe, and dppb ligands were purchased from J&K Chemical Ltd and Alfa Aesar, respectively. Unless otherwise noted, the ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. All chemical shifts are given in ppm. All coupling constants (*J* values) are reported in Hertz (Hz). High resolution mass spectrometry was measured by using an IonSpec 7.0 T MALDI-FTICRMs spectrometer. Column chromatography was performed on silica gel (100 mesh). Melting points were obtained on a Laboratory Devices Mel-Temp II instrument and are uncorrected.

General procedure for the Suzuki–Miyaura coupling through in situ phenol activation: A Schlenck tube containing a magnetic stirring bar and charged with 1-naphthol (0.5 mmol, 72 mg), PyBroP (0.75 mmol, 349.6 mg), and K_3PO_4 (2.0 mmol, 424.0 mg) was evacuated three times for 10 min under high vacuum and backfilled with N_2. Triethylamine (1.5 mmol, 0.21 mL), and dried dioxane (3 mL) were injected into the mixture under N_2 via syringe and the reaction mixture was stirred at 100 °C for about 3 h, until the 1-naphthol had disappeared, as shown by TLC. The reaction vessel was then charged with 4-methoxyphenylboronic acid **2a** (1.0 mmol, 152.0 mg) and anhydrous [$NiCl_2$(dppp)] (0.025 mmol, 13.5 mg). The heterogeneous mixture was stirred at 100 °C until the activated naphthyl phosphonium salt intermediate had disappeared, as shown by TLC. The reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by chromatography on silica gel (hexane/CH_2Cl_2 = 10:1, v/v) to give 1-(4-methoxyphenyl)naphthalene as a white solid (94.8 mg; 81 %). See the Supporting Information for characterization data and copies of the ^1H and ^{13}C NMR spectra of the coupled products.

Acknowledgements

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